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Preface

In *Advances in Drug Research, Volume* 8, Dr Barry M. Bloom, a president of an international pharmaceutical company, analyses the reasons for the drop in the *Rate of Contemporary Drug Discovery* in the USA following changes in the regulatory processes for the introduction of new medicines. Although no one would deny the duty of government to protect its citizens, excessive concern for safety may delay the discovery of improved medicines for the many diseases that are, as yet, poorly treated. Dr Bloom's comments on the difficult balance between the need for safety and the need for better medicines merit serious consideration by all concerned with the discovery, development and approval of new medicines.

Dr David Parkes, a clinician closely associated with the treatment of patients with Parkinson's disease, reviews the pharmacology, toxicology, side effects and uses of *Amantadine*. Although not as dramatic as levodopa, it is generally more effective than the anticholinergics which have been in use since the 1880's. The unrelated antiviral properties which by chance led to its use in Parkinson's disease are also reviewed.

Drugs that antagonize the actions of prostaglandins are of great scientific and medical importance. The chapter on *Prostaglandin Antagonists* by Dr Alan Bennett, a pharmacologist well known in this field, is the most comprehensive and critical review available. It is written in a way which allows quick reference to all studies with prostaglandin antagonists in a particular tissue or species, and provides an assessment of their reliability and interpretation.

The complex interrelationships of *Hypothalamic Amines and the Release of Gonadotrophins and other Anterior Pituitary Hormones* is reviewed by a neuroendocrinologist, Dr Catherine A. Wilson. The extensive literature and often controversial findings regarding the exact roles of brain amine transmitters reflect the experimental difficulties in this field. Nevertheless, there may one day be counterparts to the many useful drugs affecting peripheral transmitters, which may selectively control the release of pituitary hormones. The review of the basic physiology of the neural control of gonadotrophins may inspire a new approach to fertility control.

New classes of nonanticholinergic *Gastric Antisecretory and Antiulcer Agents* have recently been discovered. Professor Paul Bass describes the interesting and potentially useful prostaglandin analogues and the gastric antisecretory antihistamines as well as the older drugs. He poses some searching and fundamental questions.

I should like to express my thanks to the authors for the excellence of their manuscripts and to Dorothy Sharp of Academic Press Inc. (London) Ltd for upholding the high standards of book production.

July 1974 ALMA B. SIMMONDS

Contents

The Rate of Contemporary Drug Discovery[1]

BARRY M. BLOOM, PhD.

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The growing distrust our society has manifested towards science and technology in recent years has caused additional constraints to be placed upon the process of innovation through new and more stringent government regulatory policies. Though subject to government regulation in the United States for many years, the pharmaceutical industry has felt the impact of regulation increasingly since the early 1960's, and certainly in ways that constrain research.

It is now a widely accepted fact that over the course of the past decade the rate at which important new therapeutic agents have emerged from industrial drug research laboratories and become available to medical practice in the USA has slowed considerably. The likely causes of this phenomenon have been discussed and debated at length. Not surprisingly, the main parties to the debate—the regulators and the regulated—often do not agree on the causes of the decline.

There are also differing views about a more profound question: Do we really need new drugs? Some feel that the use of therapeutic drugs in our society is already excessive and the number in use might better decrease. That, of course, makes the issue out to be whether we need *more* drugs, when in fact the proper cause for concern is that we need *better* drugs.

Three complementary views are at the core of the following discussion:

1. The slow down in the rate of emergence of new therapeutic agents has grave implications for the quality of future health care, especially as regards chronic-use drugs where our need for superior new therapeutic agents is greatest—for the treatment of such leading cripplers and killers as the cardiovascular and metabolic diseases.
2. The causes of the slow down in therapeutics progress are multiple and complex. The processes by which innovative drugs have been discovered are sometimes poorly understood—unfortunately, all too

[1] Presented at the Fifth Industrial Affiliates Symposium on the Effect of Regulatory Agencies on Scientific and Industrial Productivity, Stanford University, California, November 13-14, 1972. Updated for publication in "Advances in Drug Research", 1974.

often by those in the best position to influence the situation constructively.

3. Regulatory constraints are among the most prominent factors in the recent decline of drug research productivity, although other identifiable factors are certainly significant.

This analysis of the rate of introduction of new drugs into medical practice in the USA is based on a list of the new single chemical entities—the basic new therapeutic agents—approved and marketed since 1941. The list *excludes* relatively minor products, such as new salts of old drugs, specialty dosage forms, and combinations of previously available drugs, so that it may focus upon the new therapeutic agents most significant to medicine. For the years since 1940, broken down into five-year periods, Fig. 1 shows that the rate of introduction of new

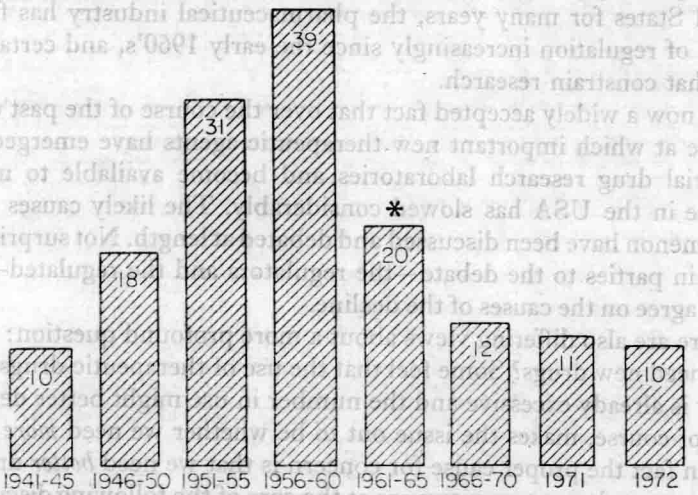

FIG. 1. Rate of introduction of new pharmaceuticals (1941–1972).
* Kefauver–Harris Amendment.

pharmaceuticals moved steadily upward, reaching a maximum during the last half of the 1950's, when new entities were being introduced in the USA at an average rate of almost forty per year. This same five-year period (1956–1960) also is unsurpassed in terms of the *medical* importance of the new compounds that emerged—the unprecedented number of innovative and useful drugs that became available in that span of time.

The sharp decline apparent in the graph coincides roughly with the 1962 passage of the Kefauver–Harris Amendments to the USA Food

and Drug Act, and more precisely with the preceding Kefauver hearings that profoundly influenced FDA regulatory practices. The net effect was a decline by half in the rate of new product emergence during the period 1961–1965, in comparison with the previous period. The rate further declined by almost half again in the most recent five-year period, reaching a low in 1969 when only seven compounds appeared on the list.

In seeking to analyse what happened during a period of dramatic progress in therapeutics to bring about such a sharp decline, the fact that major changes in the regulatory environment were taking place at that very time naturally suggests that perhaps the new regulations and the societal attitudes that brought them about were the cause.

Figure 2 details the rate of new product introductions, by drug category, for the five-year periods immediately preceding (1958–1962) and following (1963–1967) establishment of the new FDA regulations. It

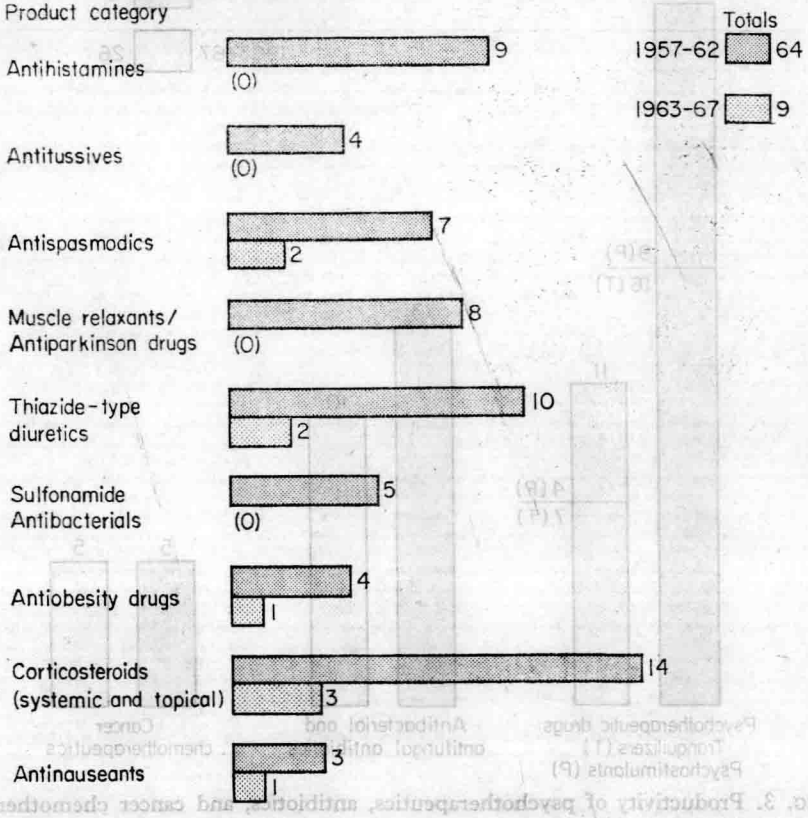

FIG. 2. New product introductions by drug category (1957–62; 1963–67).

is clear that in various well-established drug categories where a number of adequately useful agents already existed, the marketing of new products either ceased altogether or declined sharply following introduction of the new regulations.

Since the same phenomenon occurred in a number of other, minor classifications that we have *not* attempted to tabulate, one can calculate that *appreciably more than half of the decline in the rate of new product introductions that occurred after passage of the 1962 Amendments came about in this manner.*

There are a few therapeutic categories—among them some of the most important from the viewpoint of continuing medical need for superior new drugs—in which productivity has remained satisfactory, and Fig. 3 shows three such categories.

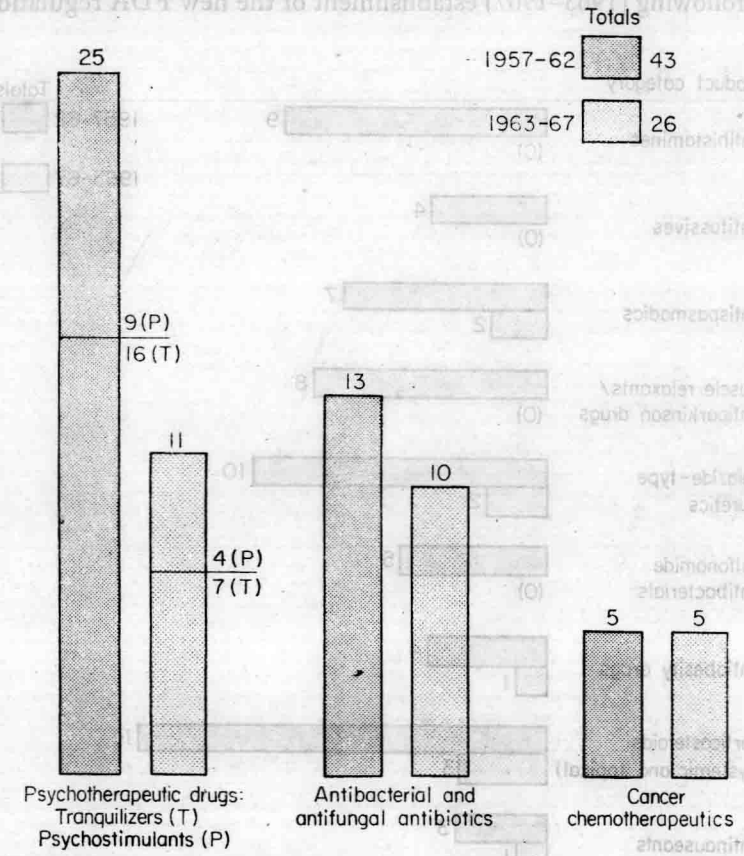

FIG. 3. Productivity of psychotherapeutics, antibiotics, and cancer chemotherapeutics (1957–62: 1963–67).

It is apparent in these specific cases that, during the five-year periods immediately pre- and post-1962, there was significantly less decline in the overall rate of appearance of new drugs, and important new medicines have continued to emerge.

But in the majority of therapeutic categories, including many of those where the need continues to be great, the rate of new product introduction in the USA declined substantially during the 1960's. An analysis of the list of basic New Drug Applications (NDA's) approved in the USA between 1966 and the end of 1972 certainly underscores this conclusion. Of the 80 basic new agents introduced during this most recent seven-year period, no less than 85 per cent were for central nervous system indications, infectious diseases, cancer chemotherapy or were corticosteroids—just four therapeutic categories.

TABLE 1

New ethical pharmaceutical product introductions 1950–1967

Year	Total new products	New single chemicals	Duplicate products	Compounded products	New dosage forms
1950	326	28	100	198	118
1951	321	35	74	212	120
1952	314	35	77	202	170
1953	353	48	79	226	97
1954	380	38	87	255	108
1955	403	31	90	282	96
1956	401	42	79	280	66
1957	400	51	88	261	96
1958	370	44	73	253	109
1959	315	63	49	203	104
1960	306	45	62	199	98
1961	260	39	32	189	106
1962	250	27	43	180	84
1963	199	16	34	149	52
1964	157	17	29	111	41
1965	112	23	18	71	22
1966	80	12	15	53	26
1967	82	25	25	32	14
TOTAL	5029	619	1054	3356	1527

Source "New Product Survey", Vol. 1 (1954) to Vol. 14 (1967), Paul DeHaen, Inc., New York, N.Y.

Obviously, during this same period, very few new drugs were introduced for the treatment of some of the most serious chronic diseases. For example: not one basic new drug for high blood pressure has obtained USA regulatory clearance (other than some diuretics) since 1963; not

one new single-entity bronchodilator has come onto the USA market since 1961;[1] not one new nonsteroidal agent for the treatment of rheumatoid arthritis has been made available since 1965.

Even before the decline in the rate of emergence of basic new agents (in fact, as early as the mid-1950's), development efforts directed towards combination products began to receive significantly less emphasis in the pharmaceutical industry. And by the early 1960's, the same proved to be the case for new dosage forms of established drugs.

These facts—fewer incremental-improvement drugs in a number of well-exploited therapeutic categories, fewer combinations and secondary dosage forms—certainly indicate that the pharmaceutical industry has increasingly been directing its research towards discovering not merely new, but more *significant* new medicines. At the same time, expenditures for worldwide research and development towards ethical human pharmaceutical products by USA-headquartered firms more than trebled, going from 207·5 million dollars to 667·9 million dollars in the period between 1960 and 1972. So it hardly seems that industry's R and D (research and development) efforts are grossly misdirected or inadequate.

It is also a fact that, due in no small measure to the far-sighted government funding policies that have bolstered USA science education and academic basic research, industrial research organizations are presently staffed with better-trained, better-equipped and more experienced research scientists than ever before.

Where then are the causes of this serious decline in research productivity? The debate over this question has been intense in recent years, generating—as such debates often do—more heat than light.

Robert Dean, an authority on government regulatory matters at Smith, Kline and French, has characterized the nature of this past debate very well:

> *The reason for the decline isn't settled. The industry points at the Food and Drug Administration as the principal cause, and the FDA points right back, citing unimaginative research as the cause. One side says drug research is strangled by bureaucratic red tape; the other says, no, it's failing because it has strip-mined the old basic research and can't seem to find a new vein. As in all such things, the truth lies somewhere in between, mired in the metaphor.*

The notion that a lack of basic biological knowledge is contributing

[1] *Author's Note* During 1973 the FDA approved cromolyn sodium, an important new drug approved by the UK CSM four years earlier, and metaproterenol (orciprenaline), approved by the CSM in 1962.

Editor's Note See "Advances in Drug Research", Volume 5, 1970, for Disodium Cromoglycate.

to the difficulty we are experiencing in bringing forth important new drugs has its advocates—but may not be entirely valid. Superior new medicines were being discovered and developed at a faster rate ten years ago than they are today; yet in the intervening years, the National Institutes of Health have channelled vast funds into basic biomedical research, up to a present-day level that exceeds a billion dollars per year. Deficiencies in our basic knowledge of disease processes and drug action do operate against the development of new drugs, but it is not logical to argue that this factor alone brought about the present decline in research productivity.

A more persuasive view is that, inevitably, successful research efforts raise the prevailing standards in a given field of drug therapy. Thus, future research in that field must aim towards progressively more difficult goals. In other words, every good new drug makes the target area for subsequent discovery efforts just that much smaller and harder to hit. Drugs like the phenothiazine and benzodiazepine tranquilizers and the tricyclic antidepressants have upgraded the quality of treatment for the various mental illnesses to the point where significant new advances in that field are much more difficult to achieve. In some categories of therapeutics, this factor undoubtedly has contributed to the slowdown in progress. But the same reasoning does not explain the absence of new drugs to treat cardiovascular, pulmonary, and metabolic diseases, fields where much present-day therapy is clearly inadequate. The reasons for lack of success must lie elsewhere.

As the USA Food and Drug Administration has moved in recent years to discharge its prime responsibility to see to it that the medicines we have in this country are pure, efficacious and safe, it has, to some degree unwittingly, created a veritable labyrinth of regulations, requirements and guidelines. To successfully traverse the labyrinth requires a research capability that on occasion comes perilously close to the limits of our present corporate and even our national medical research resources.

The precise, unequivocal demonstration of drug efficacy over long time spans, using multiple control substances, in complex disease states like hypertension, angina pectoris and atherosclerosis, to name but a few, *sometimes* calls for clinical methodology which may be still undeveloped, untried or poorly understood. It *often* calls for clinical trial protocols that tax to the utmost the ability and willingness to cooperate of both patient and clinical investigator, and which take an inordinate period to complete. If this research consistently provided a greater understanding of the drug under study of practical benefit to patients, all the effort and time required and the sizeable drain upon limited clinical resources might be justified. There is basis for doubt, however, as to whether important additional

insight is really being gained from the elaborate studies required today for the demonstration of efficacy.

Burdensome regulations can be tolerated when evaluating a new antibiotic agent, where the disease is commonly of short duration and drug efficacy is amenable to simple objective measurement. But these same regulations can prove to be the "straw that breaks the camel's back" in more complex and demanding clinical situations. This may be why useful new antibiotics are still appearing regularly, while new drugs for the treatment of hypertension are notable only by their absence.

Neither regulatory agency policy makers, industry drug research scientists, or academic medical experts appreciated the profound operational implications of this radical change in philosophy that we have undergone in recent years in regard to the assessment of efficacy of new human medicines. As Karl Beyer of Merck has put it, scientists find themselves: ". . . doing research on clinical research or on the fundamental aspects of something or other with the aid of new drugs we don't know much about. Understandably a lot of imponderables arise to confound the assessment of a drug under such conditions of investigation."

Other perceptive observers are also noticing that clinical investigation in the more complex fields is proving to be "the sticking point". Knowledgeable authorities from academic medicine, such as Louis Lasagna of the University of Rochester, have commented extensively on the nature of clinical evidence. In any given instance, they ask: What type should it be? How much is adequate? Is "more" necessarily "better"? How should it be evaluated? How much imperfection is tolerable in a clinical study?

The basic question is whether present-day requirements for "substantial evidence of efficacy" are excessive or not, when viewed in terms of what is feasible and cost-effective for present clinical methodology and resources. Increasingly, academic authorities are concluding that in some instances they are excessive. And to many observers, a basic difference in viewpoint as to what constitutes "substantial evidence" distinguished the highly regarded UK Committee on the Safety of Medicines from the FDA.

What can be done about problems such as these? To its great credit, the FDA Bureau of Drugs has come to recognize that while its prime responsibility is unquestionably to ensure to the American public that its marketed drugs are safe and efficacious, it also carries another important responsibility—to help drug research flourish in this country, thereby making useful new drugs available to medical practice as soon as possible. Commendable steps are currently being taken by the Agency, notably

their current efforts in collaboration with outside consultants to identify practical means of simplifying and speeding up the process by which the enormous flow of incoming applications undergo technical and administrative review. Also noteworthy is their intent to accept more clinical data of foreign origin, providing that it is of appropriate quality.

Yet perhaps most important of all are the recent actions taken to identify and eliminate capricious judgements and judgement-makers within the Bureau, thereby squarely confronting a serious problem long overdue for attention. Many of the assessments made by technical reviewers involve judgements that really should not be left to a single individual to make.

An area where new initiatives on the part of FDA are needed involves the earliest stages of clinical investigation. Vital questions can often be answered by single-dose, or relatively short-term experiments in man, without incurring undue subject exposure. It ought to be possible to undertake such experiments without going through the entire sequence of preclinical investigations that must and do precede more prolonged or intensive clinical trials. Without such a change, the long information feedback loops between clinic and laboratory will continue to stultify the process of discovery.

This problem has an important counterpart in the academic setting, where clinical pharmacologists, working with compounds not intended as drugs, need to be relieved of some of the burdensome Investigational New Drug (IND) paperwork and delay introduced by the FDA review process even if they contemplate only the simplest kinds of experiments in man.

The pharmaceutical company research organizations sponsoring this work also must put forth the extra effort required to turn therapeutics progress back on again. Research scientists must become more proficient at determining whether a new experimental compound has the potential to justify its further development, and when it becomes apparent that the limitations of a compound outweigh its usefulness, it must be set aside without procrastination to conserve development resources.

Despite the inordinate difficulties that such research sometimes entails, our organizations must remain determined to deliver sorely needed new medicines. The cost-effectiveness of a "breakthrough" new drug for the prevention or treatment of heart attacks and stroke or rheumatoid arthritis would be enormous. Indeed, the advent of such a medicine could probably do more than any other single event to end the use of the word "drug" in a pejorative sense.

Finally, society itself must work to turn therapeutics progress back on again—political leaders, the media, consumer advocates, and the public

at large. *Few* voices speak these days for the unfilled needs of patients with serious diseases where the potential of chemotherapy far exceeds that of other means of treatment. *Many* voices speak loudly of the risks inherent in drug research. The chorus is far out of balance, and the FDA can hardly find time from answering its many critics to exercise the sound, scientific judgement needed from it.

One can only hope that society will quickly come to realize that it is to its own great detriment to fail to place into proper perspective the problems of benefit and risk inevitably associated with the development and use of new drugs. To do otherwise would be to destroy one of the most important sources of man's well-being.