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THE ROLE OF DRUG DEVELOPMENT IN GENERATING NEW BIOMEDICAL INSIGHTS

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INTRODUCTION

In assessing productivity within the pharmaceutical industry many yardsticks are used, but one which is oftentimes overlooked is the contribution to the storehouse of scientific knowledge that occurs during drug development. The accent today on near-term output with a focus on "new single chemical entities" introduced or the number of I.N.D.'s or N.D.A.'s filed frequently overshadows other more subtle yet significant elements of efficiency which can have profound value to the scientific community and to the goal of finding new therapeutic modalities.

Related to this also is the distinction that is usually made between basic or exploratory research and applied or developmental research. The interdisciplinary and multi-dimensional relationships that exist today within biomedical and pharmaceutical research make it unwise to draw rigid lines between these different categories. There are often interconnections and feedback mechanisms which result in broad relationships and in a sense one might even classify much basic research as applied if the time horizon is extended far enough.[1] Therefore, in some respect all scientific data and outputs are valuable and contribute to the bank of knowledge

which leads to innovation and insights that can generate new therapeutic approaches and products.

DRUG DEVELOPMENT CONTRIBUTIONS

The following are a few examples of drug development programs which have contributed to the "evolving front of science" and which should be considered in any assessment of research productivity. In the long-term such output yardsticks, although difficult to quantify in terms of immediate dollar return, are no less significant than new single chemical entities, especially those which have negligible economic impact or represent a relatively minor therapeutic advance.

1) The role of dopamine in the brain and the mechanism through which this neurohormone increases adenyl cyclase in certain brain regions was not understood until the development of neuroleptic drugs. With the availability of neuroleptics such as chlorpromazine, one was able to show that these compounds block dopamine mediated increases in adenyl cyclase and lead to feedback increase in dopamine turnover; thus using neuroleptics as tools, the role of dopamine in the brain is better understood.

2) In a similar manner the role of serotonin and norepinephrine became better understood after drugs such as reserpine, which decrease these amine levels, and the various monoamine oxidase inhibitors, which increase these amine levels, were developed.

3) An important and basic physiological mechanism involved in nerve transmission, that is reuptake of neurohormones into the nerve ending, could not have been discovered without the use of amitriptyline and imipramine, two antidepressants which block this reuptake mechanism. This reuptake mechanism, which is important in terminating the action of neurohormones such as norepinephrine, would not have been elucidated without the use of these drugs.

4) The recent findings that aspirin, indomethacin, and other anti-inflammatory agents block prostaglandin synthesis has allowed the use of these drugs as tools to study the role of prostaglandin in the body. On the same subject, the mechanisms involved in platelet aggregation have recently been elucidated through the use of aspirin as an inhibitor of prostaglandin synthesis. It has been shown that an intermediate in the synthesis of prostaglandin is responsible for platelet aggregation. Without the use of an inhibitor of prostaglandin synthesis, the role would not have been shown.

5) For many years the role of gamma aminobutyric acid (GABA) has been debated and not definitely settled. Recently, it has been found that benzodiazepines in some way, either by releasing GABA or mimicking GABA action, may act through this neurotransmitter. With this knowledge and further study a better understanding of the role of GABA in the brain may evolve. Again, a drug will be used to generate insight on a basic physiological mechanism.

6) The discovery and investigational use of acetazoleamide and sulfanilamide afforded an understanding of bicarbonate resorption in renal tubular cells. The role of carbonic anhydrase in kidney bicarbonate reabsorption was not known prior to the discovery of these compounds, and the hydrogen ion:sodium ion exchange hypothesis was strengthened following their use in renal research.

In addition, it was in the search for new carbonic anhydrase inhibitors following these discoveries that the benzothiadiazides were synthesized. Many of the benzothiadiazides have little carbonic anhydrase inhibiting activity, but they have become fundamental, first-line therapy in hypertensive disease.

7) The concepts of receptor sites and neurotransmitter mechanisms is fundamental in pharmacology and medicine. The definition of α and β receptors in the sympathetic branch of the autonomic nervous system was made possible by the pharmacological use of selected sympathomimetic amines and the synthesis and use of specific and selective adrenergic blocking drugs.

Furthermore, because of the continuing synthetic effort, it has now become clear that there is more than one type of β-receptor. Butoxamine blocks β-receptors of skeletal muscle blood vessels and rat uterus, but not those of the heart and intestine, while, practolol blocks cardiac β-receptors with little or no effects on vascular or bronchiolar smooth muscle. The importance of this selectivity when treating an asthmatic is obvious.

On the other side, albuterol is a drug useful in delineating the characteristics of β-receptors in bronchiolar smooth muscle (β_2 receptors) and it has little or no action in the heart.

Without these drugs our understanding of cardiac and pulmonary physiology would be much less and our advancing sophistication in the medical treatment of disease involving these tissues would be greatly reduced.

8) During the course of investigations to obtain effective antineoplastic agents, a number of antibiotics have been found, some of which have shown clinical efficacy. These agents, in most instances, exhibit cytotoxic properties associated with inhibition of specific steps in the biosynthetic pathways of both normal and malignant cells. Using certain of these antibiotics to block specific reactions has provided a tool for studying a number of biochemical processes. For example, actinomycin D has proven very useful in selectively blocking

cellular RNA synthesis but not viral RNA synthesis in infected cells. This has allowed investigators to study the different biochemical steps involved in synthesis of viral nucleic acids and proteins without the interference of cellular RNA and protein synthesis.

9) The discovery of penicillin and subsequent developmental work over the years has resulted in the availability of a number of penicillin derivatives which have proven to be highly effective antibacterial agents. As an outgrowth of the research to improve the antibacterial efficacy of penicillin, a great deal of effort has been devoted to determining the mode of action of penicillin and its derivatives. From these studies, it has been shown that penicillin selectively inhibits cell wall synthesis at a specific enzymatic level. This information has been invaluable in helping to understand events relating to biosynthesis of the mucopeptide cell wall of bacteria and has resulted in a rational approach to chemical synthesis of other agents which can selectively inhibit cell synthesis of bacteria.

10) Recent advances in understanding the mechanisms by which antibody is produced has come primarily from the realization that families of lymphocytes exist which are specifically involved in different aspects of antibody synthesis (i.e. T lymphocytes-delayed hypersensitivity; B lymphocytes-humoral antibody synthesis). One of the few effective immunosuppressives available is azathioprine which has been shown, both experimentally and clinically, to selectively inhibit graft rejections which are exclusively associated with delayed hypersensitivity. Thus, the use of azathioprine as a specific inhibitor of delayed hypersensitivity and hence T cell differentiation, has made possible the study of B cell lymphocytes in vitro and in vivo, independent of T cell

control. These studies have helped to delineate the process by which B cells produce humoral antibody.

DISCUSSION

In the past little attention has been given to the valuable role of drug development in generating novel physiological and pharmacological insights; that is, the role of active drug development in uncovering new knowledge and broadening the frontiers of basic science. Although we usually think of new drugs emerging from the "storehouse of basic science," we tend to ignore the fact that this storehouse is often replenished from the knowledge and momentum generated by drugs during the course of their development for marketing. (Figure 1)

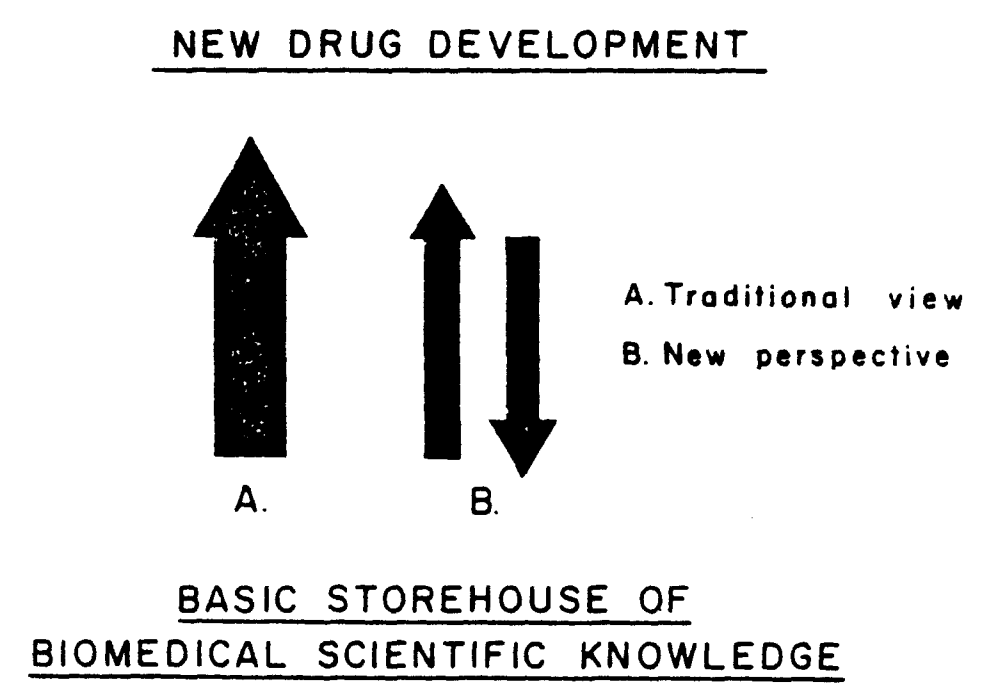

FIGURE 1 Role of drug development in contributing to the evolving front of biomedical science

In the evaluation of research efficiency and productivity within a specific firm or the pharmaceutical industry as a whole, a host of yardsticks should be used; for, if the focus is solely on narrow, easily measured parameters, such as new single chemical entities, then the very real and important contributions to the evolving front of biomedical science which occur in drug development may be overlooked.

REFERENCE

1. E. Caglarcan, R. Faust, and J. Schnee, "Resource Allocation in Pharmaceutical Research and Development," presented at the Third Seminar on Pharmaceutical Public Policy Issues, College of Public Affairs, the American University, December 15-16, 1975.