

# The First 100 Years of the Roche Group

## Leading Articles

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## Sciences towards the Medicine of Tomorrow

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Medicine, as we know it today, has been shaped by a number of comprehensive attempts to define and understand diseases and to derive from such definitions and interpretations diagnostic criteria as well as methods of therapeutic intervention. The first of these paradigmatic approaches to medicine was morphology. In contrast to other influences on medicine, morphology, anatomy, and pathological anatomy was not coming from the outside – it was synonymous with medicine itself. The human body, during the middle ages, the incarnation of a divine will, became the most prominent object for anatomical studies which ranged from realistic representations of its outer shape to careful description of the shape and the position of its organs and eventually to a complete description of its microarchitecture.

Of course, the study of architecture leads to questions regarding function and it is not surprising to see that the evolution of physiology followed the description of structure. Towards the end of the 18th and during the greater part of the 19th century, pathological anatomy emerged as a descriptive and experimental science which helped to establish a morphological (and physiological) concept of human diseases. The old ontological disease concept, which can be traced back to *Paracelsus* and *Sydenham*, found a firm basis in pathological anatomy: our classification of diseases, much of our morphological and functional diagnosis and, of course, the basic rules and strategies for surgical interventions go back to this morphological approach to disease [1][2].

### Chemical Basis of Drug Research

Drug therapy, on the other hand, as we know it today had different roots. A large part came from ancient traditional sources: morphine, quinine, salicylic acid, foxglove alkaloids and other substances could be isolated in pure form through the advances of analytical chemistry [3]. Many new heterocyclic building blocks for synthesis were found in coal tar. It is perhaps not just a coincidence in time but also in substance that the discipline of chemotherapy developed in parallel to the discovery of dyes in coal tar and to the ability of organic chemists to synthesize complicated organic molecules. *Adolf von Baeyer*'s elucidation of the structure of indigo and his subsequent synthesis of the 'king of the dye stuffs' may illustrate this statement. The reasoning of drug research and drug therapy was chemical from the beginning and it has largely remained so until today.

Terms like 'neurotropic', 'lipotropic', or 'myotropic' to describe preferential binding of dyes to neural tissue, fat or to muscle or expressions like 'haptophoric' and 'toxophoric' which were used to describe the binding parts or the toxic moieties of drug molecules, illustrate the conceptual closeness of drug research to chemistry [4]. And an overwhelming number of important drug discoveries started with chemical concepts or actual chemical substances about which empirical knowledge had been accumulated. Let us look at a few examples: In 1877, *Emil deBois Reymond*, then the most influential German physiologist wrote: 'of known natural processes

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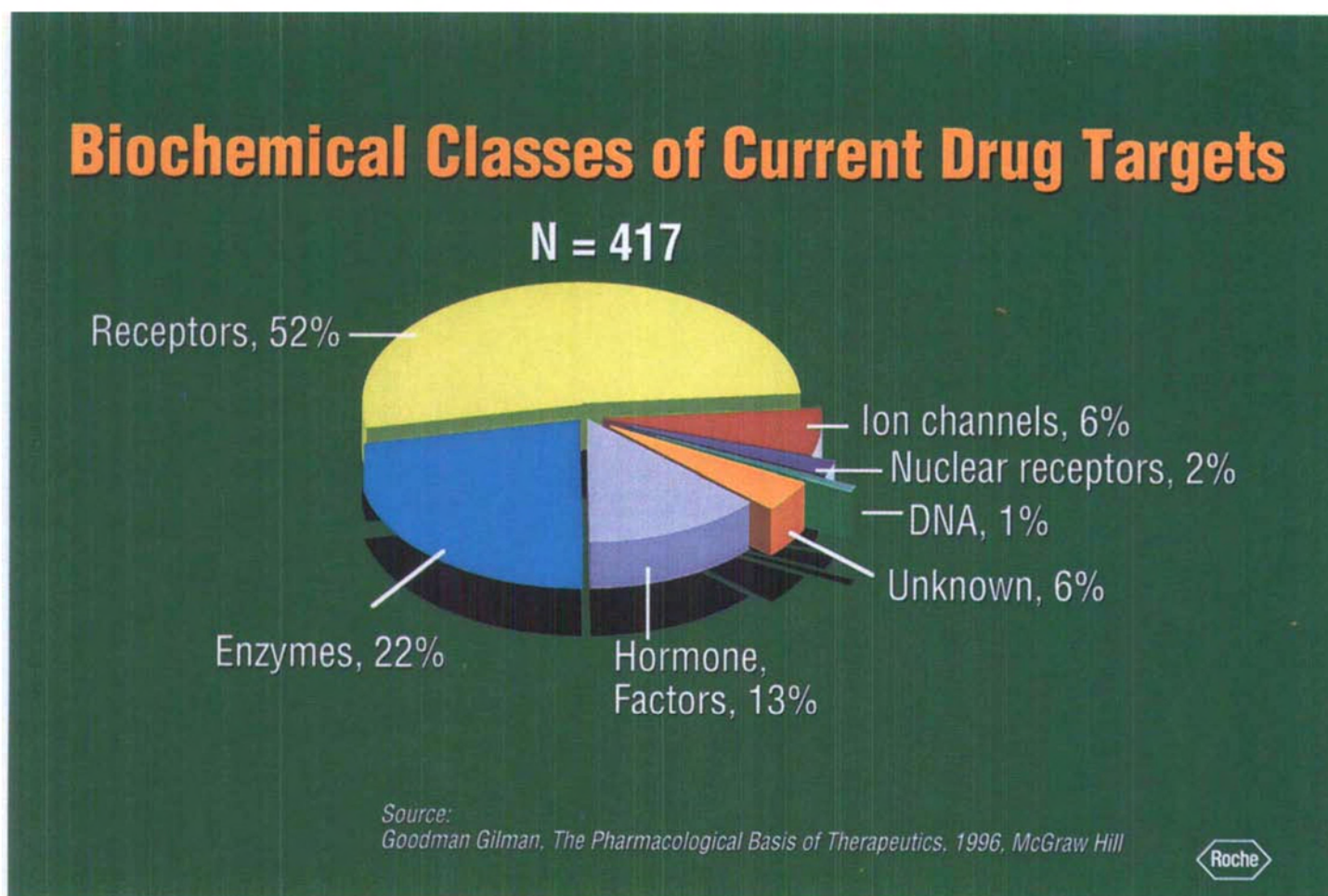


Fig. 1. Biochemical classes of current drug targets

that might pass on excitation only two are, in my opinion, worth talking about: either there exists at the boundary of the contractile substance a stimulatory secretion in the form of a thin layer of ammonia, lactic acid or some other powerful stimulatory substance; or the phenomena must be electrical in nature'. Two British physiologists, *J.N. Langley* and *T.R. Elliott*, went even further in their speculations. *Langley* in 1906: 'The stimuli passing the nerve can only affect the contractile molecule by the radical which combines with the nicotine and curare. And this seems in its turn to require that the nervous impulse should not pass from nerve to muscle by an electrical discharge, but by the secretion of a special substance at the end of the nerve.'

We know that these concepts gave rise to the experiments by *Otto Loewi* which led to the discovery of acetylcholine as the 'Vagusstoff', the substance through which vagal nerves excite the myocardium and which was later discovered to be responsible for muscular contraction at the end plates of nerves innervating muscle. *Loewi* had been extremely lucky to work with frog heart which contained little cholinesterase: very similar experiments with mammalian hearts carried out by *Dixon* had

failed because of the rapid inactivation of acetylcholine by cholinesterase [5]. We all know that the discovery of acetylcholine as a chemical transmitter led to the elucidation of mechanism of action of tubocurarine and of muscarine and provided the basis for the synthesis of neural muscular blocking agents which became so essential for the practice of modern surgery.

### Insights into Biochemical Pathways

The role of chemical substances as the initiators of new lines of drug research is even more impressive than that of chemical concepts. The benzodiazepines existed as compounds before anything was known on their mechanism of action and their clinical utility. In fact, these compounds became the probes which were used to elucidate the structure and function of GABAergic receptors and pathways. Similarly, other drugs like reserpine which had been known in India for centuries and which was even used in the treatment of psychosis and newer drugs like chlorpromazine, imipramine, iproniazide had originated from programs completely

unrelated to psychopharmacology. All of these drugs, however, became important keys which helped to understand crucial biochemical pathways. Reserpine, for instance, was used in the 1950's to treat high blood pressure and also psychiatric disorders like schizophrenia. It was noted that the drug caused *Parkinson*-like symptoms. In a series of papers, a Swedish group under *A. Carlsson* demonstrated that reserpine lowers catecholamine levels in the brain, that dopamine is one of these catecholamines and that the *Parkinson*-like effects of reserpine can be antagonized by the administration of L-dopa [6]. It was eventually shown that L-dopa restores the dopamine balance in the brain. *Bertler* and *Rosengren* later discovered that dopamine is located mainly in the *corpus striatum* [7]. Armed with this knowledge, the Austrian scientists, *Ehringer* and *Hornykiewicz* noted dopamine depletion in the brains of patients with *Parkinson's* Disease and introduced substitution therapy with L-dopa, an approach that is successfully practiced to this day [8].

Cyclosporine was found when antimicrobial metabolites were tested for immunosuppressive properties. It took a long time for the mechanism of action of this

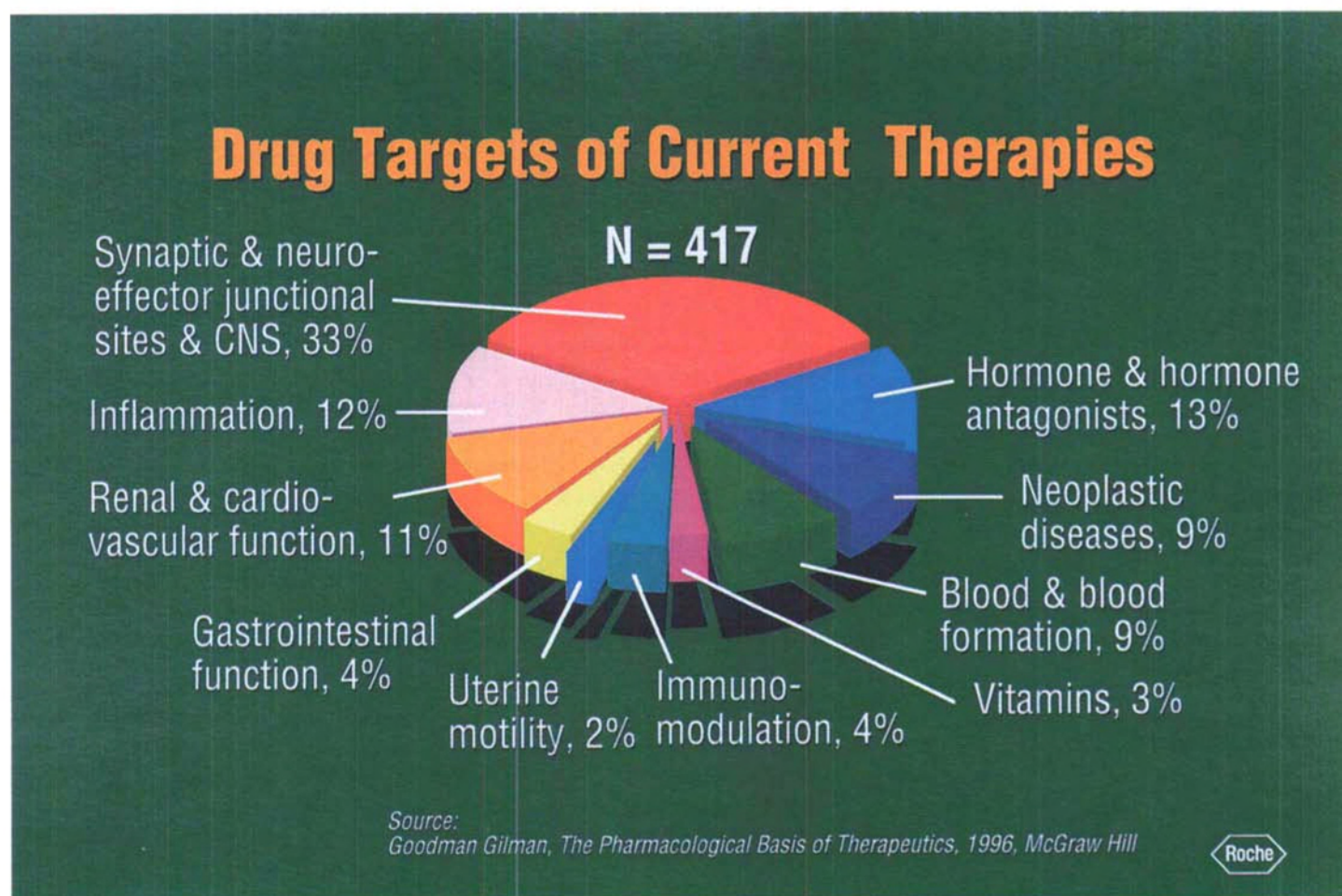


Fig. 2. Drug targets of current therapies

compound to be elucidated. Today it is known that cyclosporine inhibits calcineurin, a phosphatase which is a crucial part of an intracellular signaling pathway which eventually triggers the synthesis of IL-2. Its immunosuppressive properties were characterized long before anything was known about the molecular mechanism of its action. Today we understand how the substance works, we also understand why it is toxic and from a more complete knowledge of the signaling pathway as it evolved over the last few years, one could argue that the proteins Zap 70, Vav or NFAT 1–4 might be more selective and therefore better targets for an immunosuppressive agent.

While chemistry has been the dominant force to shape drug research, the dialogue between chemists and biologists was already a typical feature of 'chemotherapy' and became an institutional hallmark of drug research in general. In fact, the relative weight of biology in this dialogue has increased as drug research evolved. Now with genomics research in the process of elucidating the structure and eventually the function of an estimated 100 000 genes in the human genome, this relative weight is likely to increase

even further because biologists will be in a position to define potential drug targets at an unprecedented rate. If we look at drug therapy as it stands today and ask the question: how many proteins (receptors, enzymes, ion channels, carriers, etc.) are targeted by the drugs that we know today, we came up with 417 (Figs. 1 and 2). This number is based on a careful analysis of all drugs listed in the ninth edition of 'The Pharmacological Basis of Therapeutics' by Goodman and Gilman and does not include targets in viruses, bacteria, or parasites [9]. These targets were empirically found by chemical and pharmacological methods. Their utilization or choice was never based on a complete knowledge of a pathway which was relevant for a disease. Therefore, many of these targets may not be optimal. Others like the adrenergic receptor subtypes blocked by certain beta blockers or angiotensin converting enzyme may be ideal or close to ideal targets.

#### Genetic Basis of Drug Targets

How many of the estimated 100 000 human genes will turn out to be related to the multifactorial diseases that we are re-

ally interested in? When members of pharmaceutical companies talk about the number of diseases that are in need of treatment they often use the following figures: there are 30 000 known disease entities, only a few thousand of which can be treated. And then they point to the huge opportunity that still exists for drug treatment. That argument is only superficially true. There are ca. 6 000 monogenic diseases which only a few will be targets for drug therapy. There probably are many other rare multifactorial genetic diseases and rare infections. But if you take a modern textbook of medicine and list the diseases that really matter in today's world and for which treatment or improved treatment is needed, the number of such diseases is much smaller. In fact, based on latest edition of 'Principles in Internal Medicine' we found not more than 100 or at most 150 such diseases [10]. Most of these diseases are, at least in part, caused by genetic factors. And if one believes the calculations of S. Wright who started in the first third of the century to calculate the number of genes involved in multifactorial diseases like hypertension or type II diabetes, the number of genes that contribute to each of these complex disease phe-

notypes is not very high and amounts to 5–10 [11]. So if there are one hundred important multifactorial diseases, with *ca.* 5–10 genes contributing to each of them, this would give a total of 500–1000 disease-related genes.

Of course, these disease-related genes would not necessarily be good drug targets. But, if one would assume that each of these disease-related genes interacts with other proteins to form signaling pathways and that a few of them, maybe 3–10, would make good drug targets, one would come up with a possible figure of perhaps 3000–10000 interesting drug targets. Even if we assume the lower figure to be correct this would still mean that the number of drug targets could be increased by one order of magnitude from what it is today and that many of the already known drug targets would be replaced by more selective ones in the process. In other words, genomic research will add a new dimension to drug research. And, since modern chemistry will be able to respond to this substantial challenge, by generating large diverse libraries of compounds and by rapidly optimizing lead structures also through combinatorial chemical techniques, a substantially enlarged repertoire of selectively acting drugs is likely to result from the evolution of genomic sciences.

It should not go unnoticed at this point that the human genome is expected to harbor more than 10000 genes that code for secreted proteins. These secreted proteins, some of which may in themselves be drug candidates, will also be a spin-off of the genome project [12].

Other more immediate consequences of understanding the structure and function of genes would be diagnostic. For medicine such diagnostic tools will be synonymous with more comprehensive and much earlier assessment of disease risks and with the opportunity for disease prevention on a large scale.

### Summary

The continued influence of molecular biology on medicine is likely to make four major contributions:

- The assessment of individual disease risks will be greatly facilitated and will eventually become part of general medical practice.
- The knowledge of such individual risk profiles will allow for an early use of preventive strategies which will include the choice of occupation, choices of lifestyle, nutrition, preventive

surgery, drug treatment and others. From a health-economic point of view, the shift from therapy to prevention on a large scale could become the most significant result of genomic research.

- Genomics will allow to identify responders, poor- or non-responders to current medicines, this knowledge will certainly increase the effectiveness of current therapies.
- Finally, drug therapy, where necessary, will become much more selective and closer to the causes of diseases than today's therapy. Obviously, gene therapy which was not discussed in this context will greatly benefit from the further elucidation of the genetic basis of human diseases.

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