VII
Survival of the Best Fit
A Brief History of Drug-Receptor Interactions

1. Introduction

We are gathered here this evening to honor this year's Zimmer Scholar, Dr. Peter Sadler of the University of Edinburgh. In keeping with this, I have been asked by the organizers of this dinner to briefly speak to you about the early history of drug-receptor interactions, a subject that is not only closely related to Dr. Sadler's own research speciality of chemotherapy, but one in which, as we will see, the University of Edinburgh has repeatedly played a prominent role (1).

2. The Fundamental Question

The history of this subject may be viewed as the progressive unravelling of the answer to a seemingly simple question. To what extent can a chemical interaction between two reactants in a test tube (or *in vitro* as lovers of Latin would have it):

A + B → Chemical Products (*In Vitro)*

serve as a legitimate model for the *in vivo* interaction between a drug and a receptor site within a living organism?

Drug + Receptor → Pharmacological Response *(In Vivo)*

or, more specifically, to what extent do both of these processes conform to the fundamental postulate of chemistry?

$$properties = f(molecular\ composition, structure, concentration, temperature)$$

where we have subsumed both relative and absolute composition under the general label of molecular composition, and bonding topology, geometric shape, and chirality under the general label of molecular structure.

We will approach the answer to this question in three stages:

1. What are the historical origins of structure-activity relationships in pharmacology?
2. What are the historical origins of the receptor concept?
3. What is the specific nature of the drug-receptor interaction?

3. Activity and Molecular Composition

In the case of pharmacology, the fundamental postulate of chemistry reduces to the proposition that:

$$pharmacological\ activity = f(molecular\ composition, structure)_{c,T}$$

a correlation that is loosely referred to as a "structure-activity" relationship or, when quantified, as a QSAR plot, though these labels fail to properly distinguish between the two independent variables of molecular composition and molecular structure. That such a distinction is necessary becomes rapidly apparent when viewed from an historical perspective, since, prior to the 1860s only the first of these two variables – molecular composition – was accessible to the chemist.

Despite this severe limitation, several crude attempts were made in the first half of the 19th-century to correlate pharmacological activity with molecular composition alone. Thus in 1848, the British-American physician, James Blake (1815-1893), noted that the toxicity of various inorganic salts appeared to depend on either their basic (i.e. cationic) or acidic (i.e. anionic) components, but not on both. Thus $Pb(NO_3)_2$ and $Pb(C_2H_3O_2)_2$ were both toxic by virtue of their lead content, whereas As_2O_3 and $Na(AsO_2)$ were both toxic by virtue of their arsenic content, the other components of the compounds apparently playing no significant role in their observed toxicities.

Likewise, in 1864 the British physician, Benjamin Ward Richardson (1828-1896), established a correlation between physiological action and the presence of certain functional groups in simple alkane derivatives, noting that the alkyl hydrides or pure alkanes tended to function as anesthetics, the alkyl nitrites as vasodilators, and the alkyl hydroxides or alcohols as depressants.

4. Activity and Molecular Structure

It was only with the rise, in the period 1855-1875, of the valence concept, the concept of self-linking carbon chains and rings, and the concept of the tetrahedral carbon atom, that the variable of molecular structure finally became accessible to the chemist. This led, in turn, to the discovery in 1869 by the chemist, Alexander Crum Brown (figure 1) and the pharmacologist, Thomas R. Fraser (1841-1920), both of the University of Edin-

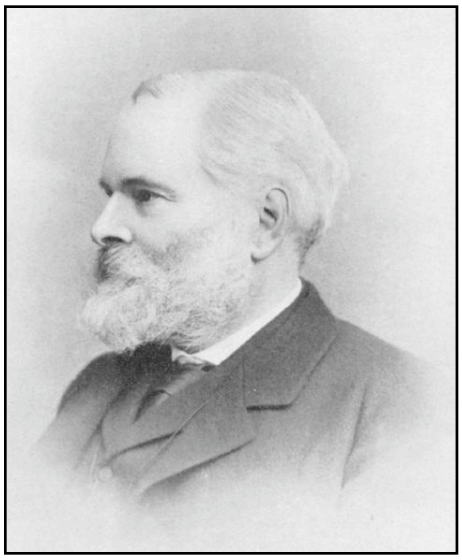

Figure 1. Alexander Crum Brown (1838-1922).

burgh, that the alkylation of tertiary amine groups in certain alkaloids:

$$(RR'R'')N + CH_3I \rightarrow (RR'R'')N(CH_3)^+I^-$$

converted them from convulsive agents into muscle relaxants, several of which, like curare, were capable of causing respiratory paralysis and death.

Crum Brown and Fraser were also the first to explicitly state the basic postulate of pharmacological structure-activity relationships and to map out a procedure for systematically applying this postulate:

There can be no reasonable doubt that a relation exists between the physiological action of a substance and its chemical composition and constitution, understanding by the latter term the mutual relations of the atoms in the substance [i.e. its molecular structure].

As some of you in the audience may know, Dr. Sadler currently holds the Alexander Crum Brown Chair in Organic Chemistry at the University of Edinburgh.

5. Activity and Molecular Chirality

In their studies of the pharmacological effects of alkylating alkaloids, Crum Brown and Fraser had, in fact, simultaneously modified both the molecular composition and the molecular structure of their test compounds. The best way to separate the effects of altering composition from those of altering structure is to study the physiological activity of a series of compounds having the same structure but variable composition. Curiously chemists do not seem to possess a generally accepted word to describe such a relationship between two compounds, though the term *molecular isomorph* (from the Greek for "equal shape") immediately suggests itself as a possibility, and, indeed, this distinction was rather imperfectly approximated in the later work of various medicinal chemists using the concept of so-called *molecular isosteres*.

Likewise, the best way to isolate the effects of altering molecular structure from those produced by altering molecular composition is to study the physiological activity of a series of compounds having identical compositions but variable structures. In sharp contrast to our previous case, examples of such a relationship between two compounds have long been recognized by chemists under the label of *molecular isomers* (from the Greek for "equal parts").

That isomers differing in their bonding connectivity (for example, diethyl ether versus butanol) often have radically different pharmacological properties soon became readily apparent, the same being true of those isomers having identical bonding topologies but different geometries (for example, *cis*- versus *trans*-dichloroethene). Far less apparent, however, was the question of whether isomers having both identical bonding topologies and identical geometries, but different chiralities, would also display significant differences. As events turned out, it was, in fact, the pharmacological study of this last class of isomers

Figure 2. Louis Pasteur (1822-1895).

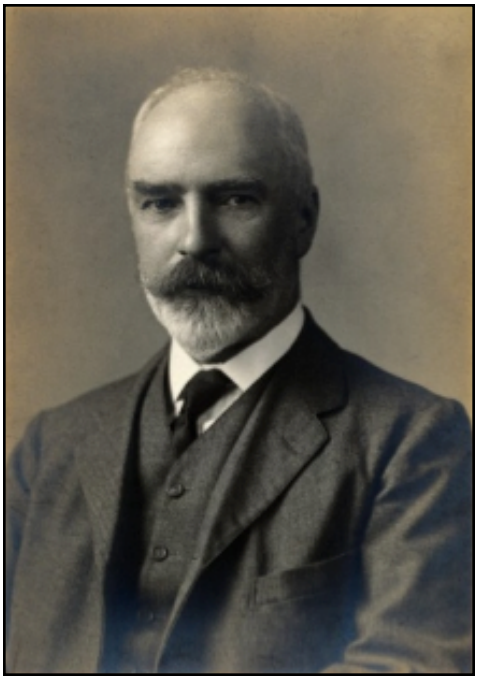

Figure 3. Arthur Robinson Cushny (1866-1926).

which ultimately gave rise to the next significant advance in the molecular theory of drug activity.

As early as 1860 Louis Pasteur (figure 2), in the course of his studies of the chirality of the tartrates, discovered that certain microorganisms were able to metabolically distinguish between chiral isomers:

d-tartrate: digested
l-tartrate: not digested

and in 1886 M. A. Piutti further observed that chiral isomers often have different tastes:

d-asparagine: sweet
l-asparagine: insipid

It was, however, the work of the Scottish pharmacologist, Arthur Robinson Cushny (figure 3), also eventually at the University of Edinburgh, on the chiral isomers of the tropane alkaloid, hysocyamine, in the period 1903-1909, which ultimately established that such isomers could also display significant differences in their pharmacological activities – results which he later summarized in his 1925 Dohme Lecture, *Biological Relations of Optically Isomeric Substances*:

l-hyoscyamine has twice the pharmacological activity of the racemic mixture dl-hyoscyamine (atropine).

Whence he concluded:

2 dl = l + d = l in pharmacological action

The inference being that the d-isomer is practically devoid of action on the myoneural junctions of the autonomic system.

6. Origins of the Receptor Concept

These results immediately raise the further question of how the body is able to distinguish between such chiral isomers or indeed of how it interacts at the molecular level with drugs in general. The beginnings of an answer to this question were first proposed by John Newport Langley (figure 4) in 1878 based on his studies of the phenomenon of drug antagonism – the fact that the administration of a drug B prior to the administration of a drug A may completely mask the normal pharmacological effects of A observed when A is administered alone and vice versa. On the basis of the antagonistic pharmacological effects of the alkaloids atropine versus pilocarpine, Langley suggested that this phenomenon was due to the fact that the two antagonistic drugs were competing for a single receptor substance within the organism:

We may, I think, without much rashness, assume that there is some substance or substances in the nerve endings or gland cells with which both atropine and pilocarpine are capable of forming compounds. On this assumption, then, the atropine and pilocarpine compounds are formed according to some law of which their relative mass and chemical affinities for the substance are factors.

Figure 4. John Newport Langley (1852-1925).

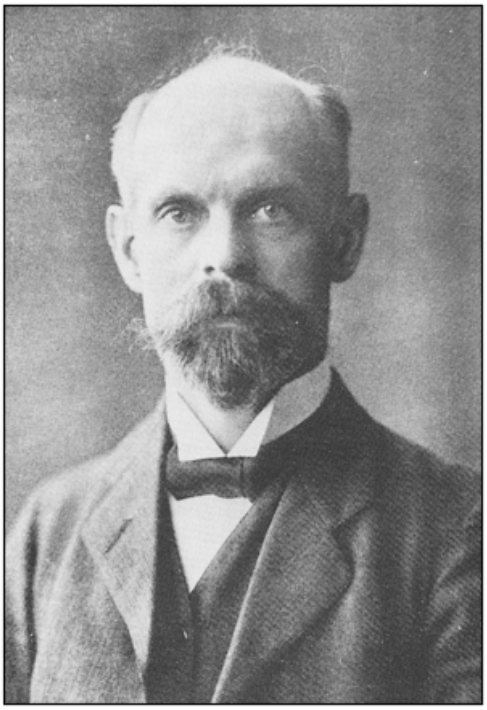

Figure 5. Charles Ernest Overton (1865-1933).

However, at the turn of the century this nascent theory of drug receptors found itself in competition with an alternative theory of drug selectivity proposed independently by Hans H. Meyer in Germany and by Charles E. Overton (figure 5) in Switzerland in the years 1898-1901. Known as the "Lipoid Theory of Cellular Depression," it was based on the observation that the depressant effect of a wide variety of drugs failed to correlate with the presence or absence of certain functional groups or structural features but did correlate with their relative solubilities in lipids, as measured by the distribution of the drug between an aqueous phase and a lipid phase, usually represented by olive oil. In other words, drug activity depended more on relative solubility in a lipid phase, and hence on the ability of the drug to penetrate the cell, than it did on stereospecific interactions with a hypothetical receptor site within the cell.

The lipoid model said little or nothing about the phenomenon of drug antagonism or about the possible existence or nonexistence of drug receptors, though it did seem to momentary divert attention from the further development of these concepts. Consequently in 1905 Langley once more put forth an elaborated version of his receptor theory, this time based on an experimental study of the antagonistic action of nicotine versus curare.

Two years later, Paul Ehrlich (figure 6), stimulated by Langley's recent work and by his own studies of the specificity of drug resistance in microorganisms, completed the picture by extending his earlier "side-chain theory" of antibody interactions so as to include drug interactions as well. This he did by explicitly postulating the existence of specific "chemoreceptors" on the surface of cells capable of chemically interacting with certain "selective groups" on the drug molecule itself.

7. The Nature of the Drug-Receptor Interaction

But exactly how did these postulated "chemoreceptors" discriminate between one chiral isomer and another? Cushny, in his studies of the selectivity of chiral isomers, thought that the receptor site was also chiral and that it reacted indiscriminately with both drug isomers to produce achiral products which differed significantly in both their physical and pharmacological properties:

There can, I think, be no question that ... the differences observed between the two optical isomers arises from the same cause ... that is, because in the tissues, as in the test tube, the isomers form compounds with some optically active substance and these compounds are no longer identical in their physical characteristics.

If this were really true, then the pharmacologically inactive *d*-isomer should automatically act as an an-

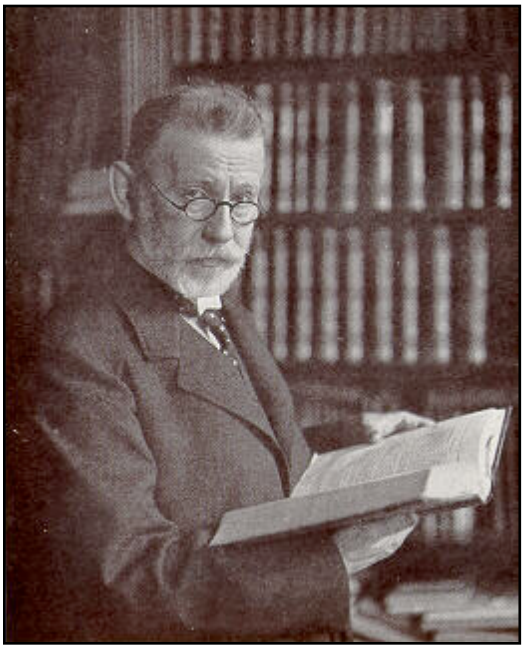

Figure 5. Paul Ehrlich (1854-1915).

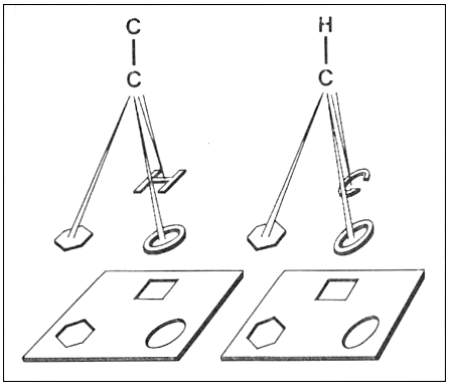

Figure 7. A receptor surface must require a drug to simultaneously bind at three distinct sites before it is able to discriminate between one chiral isomer and another.

tagonist for the pharmacologically active *l*-isomer, which wasn't the case. Rather, in keeping with the Langley-Ehrlich receptor model, the receptor site should instead selectively interact with only the pharmacologically active *l*-isomer but not with the inactive *d*-isomer.

Though later authors vaguely hinted that the required selectivity was probably based on some stereochemical "lock and key" mechanism, like that postulated earlier by Emil Fischer for enzyme interactions, the exact nature of the lock and key was left unanswered until 1933 when Leslie Easson and Edgar Stedman of the Department of Medicinal Chemistry of the University of Edinburgh proposed their "three-point contact" lock and key mechanism for receptor discrimination of chiral isomers (figure 7), though widespread acceptance and application of their theory would not occur until the 1950s.

8. Conclusion

In conclusion, I would like to thank you of the audience for tolerating a talk on a subject which is rather more academic than is the norm for the average after-dinner speech. If nothing else, I hope I have convinced you that Dr. Sadler's chosen field of chemotherapy has a rich and interesting history and that, in taking up his present position at the University of Edinburgh, he has associated himself with an institution that has distinguished itself more than once in the field in question.

9. References and Notes

1. A lecture given at the Zimmer Symposium Dinner in Honor of Dr. Peter Sadler of the University of Edinburgh, held at the University of Cincinnati on 28 April 2006.

2. In preparing this talk I have drawn heavily on the pioneering historical work of John Parascandola on the history of pharmacology, including the following publications: J. Parascandola, "Structure-Activity Relationships – The Early Mirage," *Pharm. Hist.*, **1971**, *13(1)*, 3-10; J. Parascondola, R. Jasensky, "Origins of the Receptor Theory of Drug Action," *Bull. Hist. Med.*, 1**974**, *48*, 192-220; J. Parascandola, "Structure - Activity Relationships in the Early Twentieth Century," *Pharm. Hist.*, **1974**, *16(2)*, 55-63; and J. Parascondola, "Arthur Cushny, Optical Isomerism, and the Mechanism of Drug Action," *J. Hist. Biol.*, **1975**, *8*, 145-165.