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Commentary

Fifty years of *Biochemical Pharmacology*: The discipline and the journal

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ABSTRACT

The discipline of biochemical pharmacology emerged in the late 1940s as a result of an increasing emphasis on understanding drug mechanisms at the cellular level. This research approach has contributed significantly to the development of many new drug classes including antihypertensive, antifective, cholesterol lowering, anti-inflammatory, and anticancer agents, as well as antipsychotics, antidepressants and anxiolytics. Biochemical pharmacology remains a major tool in drug discovery, being employed in the search for novel therapeutics for the above and other conditions and clinical challenges, such as neurodegenerative disorders, for the treatment of pain, and for development of agents that do not induce, or can overcome, antibiotic/antiviral resistance. Together with chemical, molecular, genetic, physiological, and clinical sciences, biochemical pharmacology will in the coming decades continue to be a critical component of the drug discovery process.

1. Introduction

Two milestones in the history of pharmacology are being celebrated this year. One is the 100th anniversary of the founding of the American Society for Pharmacology and Experimental Therapeutics (ASPET) by J.J. Abel [1] and the other is the 50th anniversary of *Biochemical Pharmacology*. The journal was created to document "research into the development of biologically active substances and their mode of action at the biochemical and cellular level" [2]. Founded by the pioneering oncologist Peter Alexander [3] and colleagues in 1958, the launch of *Biochemical Pharmacology* was: (i) *coincident* with the emergence of a number of technologies developed during World War II that facilitated the ability to make more precise and reliable measurements in biological systems that found ready application in biomedical research and; (ii) *congruent* with the biochemically based advances in the understanding of enzyme structure and function and natural product synthesis in the 1940s, the latter of which led to the facile, fermentation-based production of penicillin [4].

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Abbreviations: ACE, angiotensin-converting enzyme; RAS, renin–angiotensin system; SARs, structure–activity relationships; NSAIDs, nonsteroidal anti-inflammatory drugs; NCEs, novel chemical entities; RA, rheumatoid arthritis; VRSA, vancomycin-resistant *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

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The emerging discipline of biochemical pharmacology provided the means therefore to initiate the search to identify the molecular targets through which drugs and other bioactive compounds produce their effects on normal and diseased tissue. This initiated the efforts to provide a systematic molecular framework for defining more precisely disease causality and the mechanisms whereby drugs provide therapeutic benefit(s). It was another 40 years, however, before this concept became reality with the cloning of a variety of genes, including those responsible for the production of hormone and neurotransmitter receptors [5,6]. Besides representing some of the most important targets for drug action, receptors have been a major topic of interest for biochemical pharmacologists.

1.1. *Receptor concepts*

From the mid 19th century until the early 20th, the empirical and physiological techniques perfected by Claude Bernard to study the effects of xenobiotics on tissue function [6] provided the intellectual context necessary for the development of the 'lock and key' theory of drug action. While the concept of 'receptive substances' is ascribed jointly to J.N. Langley and Paul Ehrlich at the turn of the 20th century [7,8], the former may have first suggested the idea as early as 1858 [9]. Receptors are macromolecules present both on the surface of, and within, the cell. Over time this term was used to describe every conceivable drug target including enzymes, DNA binding motifs, RNA and protein/protein interactions. This formalized further the concept of molecular targets at which the 'magic bullets' obtained from both synthetic and natural product sources produced their effects, both beneficial and detrimental.

The receptor concept was initially proposed on the basis of the actions of compounds in bioassays or in animal models in the total absence of any direct physical evidence for their existence [10]. This early deficiency notwithstanding, the concept has been the basis for understanding disease causality and drug actions for over a century [8], and continues to guide the search for new therapeutics.

When first proposed, the receptor concept was more qualitative than quantitative in nature and therefore met with considerable resistance from prominent pharmacologists, including Rudolf Magnus and Henry Dale [10,11]. Indeed, Dale considered the receptor concept a ''cloak for ignorance'' [9]. It was not until the 1930s that A.J. Clark and John Gaddum provided crucial support for the receptor theory by undertaking a quantitative analysis of drug action [8,12]. While the subsequent work of H.O. Schild, Everhardus Ariens and R.P. Stephenson elaborated on the work of Clark and Gaddum, it was the seminal work of Raymond Ahlquist in 1948 [13] attributing the different pharmacodynamic effects of epinephrine to different types of adrenoceptors, α- and β, that became a seminal point in the acceptance of the receptor theory as a basis for drug action [10,14]. The subsequent work of Bjorn Folkow, Georg Kahlson and James Black on adrenergic and histamine receptor subtypes [15] led to the successful development of propranolol, a β-adrenoceptor antagonist, and cimetidine, the first of the histamine H_2 receptor blockers. Both of these agents were developed utilizing a cyclical iteration to assess compound activity at the biochemical target that entailed a close working relationship between medicinal chemists and pharmacologists in defining structure–activity relationships (SARs) [16].

Historically, few of the quantal iterations in the conceptualization of receptor function have been readily embraced by pharmacologists. For example, the concepts of transmitter co-release [17], allosteric modulation and ligand efficacy, including inverse agonism and constitutive activity [8,9], were all met with varying levels of skepticism by those in the discipline. As a group, pharmacologists may be viewed as highly conservative, although sufficiently objective to ultimately succumb to the persuasive power of data.

1.2. *Biochemical pharmacology*

By studying the effects of novel chemical entities (NCEs) on tissue and cellular function, it became possible to define more precisely the causes of human disease at the molecular level and to, in turn, develop safer and more efficacious drugs for the treatment of these conditions. This biochemical approach to drug discovery predominated from the early 1950s until the late 1980s. These techniques proved highly successful in the development of new therapeutics. Among the novel drug classes identified with this approach were antidepressants, antipsychotics, β-adrenoceptor antagonists, loop diuretics and angiotensin converting enzyme inhibitors [15]. While the emphasis on biochemical pharmacology as a tool in drug discovery declined over the past two decades with the ascendancy of molecular biology [18,19], the interest in examining drugs and drug candidates at the biochemical level has been rekindled in recent years under the rubric of chemical genomics/genetics. Thus, once again, NCEs are being used to characterize or modify drug targets and targets are utilized to characterize the efficacy and selectivity of NCEs *in vitro* before advancement into more costly and complex *in vivo* animal models [20,21].

Two fundamentally important concepts arose from the era of biochemical pharmacology. The first was that knowledge of the mechanism of action of an NCE is critical in defining the agent. Using biochemical techniques, NCEs were iteratively evaluated and optimized for potency, efficacy and target selectivity *in vitro* at defined molecular targets before being tested in more complex tissues, organ systems or intact animals. This approach made possible the rapid identification of the most promising candidates independent of the variables associated with their pharmacokinetic differences. Historically, drug mechanisms were defined in organ systems or in whole animals by determining structure–activity relationships of a series of agonists and antagonists to assess effects on phenotypes. The results of these studies were often ambiguous as many of the test agents were nonselective in their effects and because differences in response were often more the result of pharmacokinetic rather than pharmacodynamic properties. Testing an NCE *in vitro* at a known molecular target made it possible to more precisely characterize its ability to interact selectively at this site independent of its other properties, thereby enhancing the characterization of the compound and the receptor system under investigation. This led to a somewhat naïve variation on

Descartes 17th century postulate, ''I think, therefore I am''. For receptor ligands, the corollary less elegantly became ''I was conceived as a specific agonist for receptor *x*, therefore I am a specific agonist for receptor *x*''. With the advent in 1975 of facile, increasingly high throughput, receptor binding assays [22], target-derived structure–activity studies for NCEs became increasingly reductionistic, reaching the ultimate goal when compound selectivity could be obtained in recombinant systems enriched by transfection of a single drug target [23].

The second concept that evolved from biochemical pharmacology was that this approach was most powerful when used in conjunction with, and as an extension of, an empirical, physiology-based research program rather than being a wholesale replacement for these more traditional techniques. This contrasts with the exclusionary use of molecular biology in a technique known as synthetic biology [24]. This approach focuses on examining drug sites of action and disease processes using target cloning, recombinant protein expression and target mutations to create engineered cell lines and animals. While synthetic biology was designed to replace the pharmacologically based approach, its utility is limited because NCEs optimized in engineered cells and organisms, such as single target expression systems, ultimately require evaluation in native systems where ancillary proteins, both known and unknown, can markedly influence target recognition and functional events [25]. For example, the scaffold for the glutamic acid NMDA receptor has some 90 associated proteins [26], any one of which could influence the interaction of an NCE with the receptor.

The synthetic biology approach to drug discovery was complimented at the turn of the 21st century by the genomic phase of pharmacology. Based on the draft maps of the human genome [27,28], the genomic phase was driven by an expectation, so far unrealized, that defining disease-associated genomic targets, their proteomic progeny and related interactomic pathways would provide the means to more efficiently and accurately determine the causes of human disease and thereby more rapidly lead to the discovery of novel therapeutics. In theory such drugs would be highly specific in their disease-related, beneficial effects and therefore safer and more efficacious than existing agents [29]. Given the lack of success with this technique, some view with great skepticism the promise of the genomic approach as a primary method for drug discovery [30].

1.3. *Target validation*

While the genome-based approach to drug target identification is heuristically engaging, a major challenge in its reduction to practice is the need to validate newly identified drug targets and disease-associated molecules in patient populations. However, the concept of target validation [31–33] is subject to different interpretations and remains controversial. The most logical endpoint in target validation is the identification of NCEs that are potent and selective for the selected site, have drug-like properties, and demonstrate benefit in patients with a disease associated with that target. This is a lengthy and expensive proposition. While it has been proposed there are points in the standard process of NCE advancement where a target can be validated [31], there are many instances where NCEs extensively validated in preclinical models produce no effects in humans. Notable examples include neurokinin-1 receptor antagonists as analgesics and antidepressants [34], the ampakine, CX516, as a cognition enhancer add-on therapy for antipsychotic treatment [35], and the thousand or more putative neuroprotectants developed for the treatment of stroke [36]. Accordingly, many believe that anything short of a proof of concept in the clinical population should more appropriately be viewed as a process of enhancing confidence in the target as opposed to its validation [37].

2. Pharmacology in the 21st century

Since its beginnings as a distinct branch of biomedical science, pharmacology has been synonymous with drug discovery, both from the perspective of being key to the discovery of potential new drugs and in defining the mechanisms of action of existing agents. Pharmacological studies have also been important in advancing the understanding of human disease, which in part accounts for it being a central component in the National Institutes of Health (NIH) Roadmap Initiative [38,39].

To a major, if not exclusive, extent, pharmacology is an interdisciplinary and interrogatory discipline that utilizes hypothesis-driven experiments focused primarily on understanding tissue function and diseases in the context of drug responses. As such, pharmacology is generally independent of a technology platform-driven approach. Thus, rather than developing a new technology and then finding uses for it, pharmacologists propose hypotheses and then employ multiple techniques, both new and old, to test these theories. A highly goal oriented discipline, pharmacology is characterized by the use of a critical path approach to maintain focus on resolving the therapeutic question being addressed. This is in marked contrast with the current focus on targets that may be termed 'targophilia'—an obsession with, and excessive focus on, sites of drug action to the exclusion of physiological function.

Provided below is a brief overview of contributions made to drug discovery by pharmacologists in general, and biochemical pharmacologists in particular, during the past half-century.

2.1. *Cancer chemotherapy*

For many years, oncology drug development was focused on cytotoxic agents like the nitrogen mustards [40] that block important functions vital to the survival of dividing cells. Such drugs have largely pleiotropic effects. Also included are DNA-damaging agents like cisplatin and mitomycin C, inhibitors of microtubule polymerisation, such as taxol, antimetabolites like methotrexate and 5-fluorouracil, and topoisomerase inhibitors that affect DNA structure [41]. While all are efficacious, their lack of selectivity renders them toxic although some newer alkylating agents like bendamustine show improved efficacy with more manageable side effects [42]. Moreover, resistance frequently develops to the therapeutic effects of such agents after initial stabilization or disease regression. Alternative approaches to cancer therapy

include antihormonal agents such as estrogen-receptor modulators [43,44] and aromatase inhibitors [45]. These agents target cellular functions essential for proliferation of specialized tissues such as the breast epithelium.

Over the past decade, chemotherapeutic agents have also been developed for targets thought to be important in cancerous cells. These included inhibitors of various kinases in the human kinome [46,47], the ATPase/chaperone family [48], the proteasome [49], and histone deacetylases (HDACs) [50,51]. The latter two drug groups are of particular interest. While regulated protein degradation is an essential aspect of cellular homeostasis, biochemical studies have revealed altered functions for the components of the ubiquitin-proteasome system (UPS) in cancer [49]. Examples of UPS gene modifications involve the linking of ubiquitin to tumor-suppressor proteins, and to proteins involved in DNA repair and genome integrity. Positive clinical data were obtained with the first generation proteasome inhibitor, bortezomib, in the treatment of multiple myeloma [52]. HDAC inhibitors can reverse the aberrant epigenetic changes associated with cancer killing tumor cells at very low concentrations *in vitro*. While inhibitors such as SAHA are efficacious as monotherapy, their pleiotropic anticancer activities suggest they will also be used in combination with other agents [51,53].

A major breakthrough in the treatment of cancer has been the development of kinase inhibitors that block constitutively active kinases or those playing a key role in tumor cell growth, *e.g.*, c-Src, c-Abl, b-Raf, ALK, MAP, PI3K. AKT, VEGFR and EGFR [47]. Inhibitors of cyclin-dependent kinases [54], Aurora kinase [55] and the tyrosine kinases, c-Abl (imatinib), HER2 (trastuzumab), VEGF (bevacizumab), EGF (gefitinib, cetuximab) and bRaf (sorafinib) have revolutionized the treatment of cancer with selective agents being used for the 'personalized' treatment of targeted cancers resulting in safer, more effective agents. Genetic 'fingerprinting' of a tumor can greatly facilitate the choice of the appropriate drug regimen and the treatment outcome related to survival. The success of imatinib (Gleevec) in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors has provided proof of the often criticized postulate that a better understanding of cancer at the biochemical and molecular levels is essential for the development of more effective and less toxic drugs [56,57]. Unfortunately, many CML patients receiving imatinib continue to display residual disease or develop resistance because of mutations in the kinase domain. Second generation BCR-ABL inhibitors, such as nilotinib and dasatinib, appear to be more efficacious than imatinib, but are still subject to the development of resistance, being relatively inactive following the BCR-ABL T315I mutation. Inhibitors with a potential to overcome this resistance have yielded encouraging results in preliminary clinical trials. Like many tyrosine kinase inhibitors, imatinib shows only relative selectivity in its actions also inhibiting TEL-ARG, PDGF and c-Kit [57]. Second generation tyrosine kinase inhibitors include gefitinib, erlotinib, sorafenib [58] and sunitinib [59].

Biochemical pharmacology studies have revealed that the PI3K/AKT/mTOR (mammalian Target of Rapamycin) pathway is dysregulated in many tumors [60] through a loss of PTEN function, amplification of the PI3K p110 subunit, mutation of the p85 regulatory subunit of PI3K, amplification of AKT1 and 2, and mutation of mTOR regulatory proteins, such as TSC1 or TSC2 [60,61]. Approved mTOR inhibitors include rapamycin and temsirolimus with others in development.

2.2. *Anti-infectives*

The success of the sulfonamide antibiotics (1936), followed by that of the β-lactams (1940), including the penicillins, cephalosporins, monobactams and carbapenems, the tetracyclines (1949), chloramphenicol (1949), the aminoglycosides (1950), the macrolides (1952), glycopeptides (1958), the quinolones (1962) and streptogramins (1962), represented a golden age of antibiotics [4,62,63]. These discoveries led the U.S. Surgeon General to state in 1972 that "the book of infectious diseases can now be ultimately closed". This observation unfortunately failed to take into account antibiotic resistance [64,65] that results from indiscriminant use of these drugs in humans and farm animals. Today 70% of the bacteria that cause hospital infections are resistant to at least one antibiotic, with some organisms being unresponsive to all approved agents. Vancomycin-(VRSA) and methicillin-(MRSA) resistant forms of *S. aureus* are the most common antimicrobial drug-resistant pathogens in American hospitals and have now spread to the community. *S. aureus* resistance to the oxazolidinone antibiotic, linezolid, introduced in the 1990s, was reported in 2003. Given these developments, a great deal of anti-infective research has focused on developing new drug classes to treat VRSA and MRSA [63,66], with platensimycin, isolated from *S. platensis*, having recently been introduced for this purpose [67]. Platensimycin is a potent, broad-spectrum Gram-positive agent that acts by inhibiting cellular lipid biosynthesis. Because of its novel mode of action, platensimycin does not display cross-resistance to VRSA and MRSA, or vancomycin-resistant *Enterococci*. The incidence of antibacterial resistance has stimulated efforts over the past decade to develop new classes of antibiotics, with particular emphasis on examining bacterial genomes to identify novel targets unique to these organisms [53,65,68].

Progress has also been made in developing antiviral therapies, including drugs for the treatment of herpes simplex [69], AIDS (HIV) [70], hepatitis [71,72], and influenza [73]. Examples include HIV protease inhibitors. The current research focus in this area is on RNA viruses [74]. Much of this progress has been aided by genome sequencing and structure-based drug design [70]. The potential of bioterrorism represents another frontier in anti-infective drug discovery [75,76].

2.3. *Cardiovascular therapeutics*

Over the past 50 years new drugs have led to a remarkable reduction in the morbidity and mortalities associated with cardiovascular disease. These include the β-blockers, calcium channel blockers, modulators of the renin–angiotensin system (RAS) and modulators of cholesterol synthesis [77,78]. These agents all resulted from biochemical and physiological studies aimed at defining the pathways and systems responsible for the regulation blood vessel tone and integrity, cardiac and renal function, and reducing cardiovascular risk by normal-

izing blood pressure, preventing thrombosis and atherosclerosis, or regulating fluids, electrolytes, or heart rate [79].

The catecholamines norepinephrine and epinephrine that are released from sympathetic nerve terminals and from adrenal glands, respectively, regulate vascular tone through actions at α-adrenoceptors and heart rate by β-adrenoceptor stimulation [78]. The pioneering work of Ahlquist [13] and that of James Black, Bill Duncan and colleagues led to the development of α-adrenoceptor antagonists for the management of hypertension and β-adrenoceptor antagonists for treating hypertension, cardiac arrhythmias, cardiac ischemia and heart failure [80,81]. Adrenoceptor agonists are also in use for the treatment of asthma, cardiogenic shock, hypotension and benign prostatic hyperplasia. Verapamil, nifedipine, diltiazem and amodipine block distinct ion channels to reduce arterial pressure in individuals with severe hypertension who are non responsive to β-blockers or diuetrics [82,83].

The kidney plays a key role in regulating blood pressure by modulating renal blood flow, sodium and water filtration [84]. The first group of antihypertensive drugs acting through the kidney were the diuretics [85]. This included the loop diuretics, amiloride, a potassium-sparing diuretic and the various thiazides that inhibit Na^+/Cl^- reabsorption from the distal renal tubules. These, like the calcium entry blockers, provided an additional therapeutic option to lowering blood pressure, alone and in combination with other antihypertensive agents [86].

The RAS reflects a cascade of biochemical events initiated by release of the enzyme renin from the kidney in response to changes in renal blood flow, sodium filtration or sympathetic nervous system activity. Once released, renin is involved in the production of angiotensin II, a potent vasoconstrictor that increases blood volume by stimulating the release of aldosterone from the adrenals which, in turn, acts on the kidney to increase fluid retention and elevate blood pressure [87]. The pioneering biochemical studies of Miguel Ondetti and David Cushman [88] identified the active site of angiotensin-converting enzyme (ACE) that catalyzes the formation of angiotensin II from angiotensin I using a mixture of bradykinin-potentiating factors isolated from the venom of the snake, *Bothrops jararaca*. This eventually resulted in the successful development of the first ACE inhibitor, captopril. Concurrently, studies on angiotensin II receptors yielded partial agonists and antagonists [89] that together with the ACE inhibitors became standard therapies for the treatment of hypertension, with proven benefits in reducing the incidence of strokes, heart attacks, renal and heart failure. More recently, aliskiren, a renin inhibitor, was approved for the treatment of hypertension [90]. Drugs modulating the RAS represent a major accomplishment of biochemically based research that has revolutionized the management of cardiovascular risk and disease.

Biochemical pharmacology also played a major role in the discovery and development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors for the treatment of atherosclerosis [91]. This research was driven by the identification of natural product inhibitors of this enzyme, a key step in cholesterol synthesis, and by data suggesting an association between high blood cholesterol and the risk for adverse cardiovascular events, including heart attack and strokes [92,93]. Using biochemical screens, optimization of these early leads led to mevastatin, the first of HMG-CoA reductase inhibitor to demonstrate therapeutic potential. Second generation statins include simvastatin, atorvastatin and rosuvastatin.

Large-scale human trials indicated that the statins not only reduce blood cholesterol but the risk for heart attack, stroke, and other forms of atherosclerosis-related cardiovascular disease [93]. In recent years this drug class has become established as the standard for reducing cardiovascular risk in diverse patient populations, including those with metabolic syndrome and diabetes [91]. Other classes of lipid lowering agents include fenofibrate, which activates peroxisome proliferator activated receptor-α, enhancing fatty acid oxidation and reducing triglyceride levels [94], and ezetimibe, which inhibits cholesterol absorption from the small intestine by attaching to Niemann-Pick C1-like protein [95]. When used alone ezetimibe is only modestly effective in reducing cholesterol and is therefore often given in combination with a statin. These biochemically based research efforts have yielded innovative therapeutics that are routinely used for the management of dyslipidemias, contributing significantly to the reduction in cardiovascular disease.

2.4. *Neuropharmacology*

Up until the 1950s there were few medications developed specifically for the treatment of neurological and psychiatric disorders, and those that were employed were often of homeopathic origin. Serendipitous discoveries, such as the effectiveness of lithium, an ion once used to treat epilepsy, gout and cancer, in the treatment of manic-depressive illness, the identification of iproniazid, an anti-tubercular, as an antidepressant, chlorpromazine for the treatment of schizophrenia, and diazepam for anxiety, revolutionized the care of psychiatric patients [15]. However, it is noteworthy that the mechanisms of action for three of these four agents were only discovered after they were found to be effective in humans. The mode of action of the fourth, lithium, remains controversial to this day. While these early drugs were discovered through empirical observation, over the past 50 years central nervous system (CNS) drug discovery, like all therapeutic areas, has moved towards a more focused mechanism based approach for identifying new agents. This has resulted in the discovery of transmitter-selective monoamine uptake inhibitors, such as fluoxetine [96], and metabotropic glutamate 2/3 receptor agonists [97]. However, with a few notable exceptions, the major focus of research remains on synthetic iterations of the prototypic dopamine D2-receptor blocking antipsychotics [98], the benzodiazepine anxiolytics [99], and monoamine uptake inhibitors [100,101], with serendipity still playing a major role in the discovery of something truly novel. Progress has been especially slow in identifying drugs capable of arresting the underlying disease processes associated with neurodegenerative disorders, such as stroke [36], Parkinson's [102] and Alzheimer's diseases. With regard to Alzheimer's disease, the hypotheses that β-amyloid and/or tau hyperphosphorylation [103,104] are causative remain unproven, with a multitude of theoretical therapeutic approaches awaiting reduction to practice [105]. For example, work continues on

the development of an Alzheimer's vaccine that clears β-amyloid [106].

Substance abuse is another area where significant challenges remain in developing medications for a societal problem that grows relentlessly each year [107,108]. The success of varenicline, a $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, in smoking cessation [109], and its potential utility in treating alcoholism [110], has reinforced the notion of developing substitute ligands for drugs of abuse [111] that differ from the abused agent in their mode of association with the target site. Both partial agonists and allosteric modulators represent ligands of this type [112].

Few pharmacologists in 1958 looking toward the 21st century would have expected that the mainstays of analgesic therapy would still be the opioids. Even fewer would have thought that, following the isolation of the opioid receptor family in the mid 1970s [113], and the massive infusion of resources from the pharmaceutical industry in attempts to exploit this finding, that a plethora of new analgesics would not have entered the marketplace. Given the identification of the opioid receptor family, and the biochemical techniques available for screening large numbers of drug candidates, it was anticipated that in a relatively brief period of time analgesic NCEs that are selective in their actions but devoid of the respiratory depressant, euphoric and constipating effects of opioids would be found. Unfortunately, this promise remains unfulfilled despite [114]. As a consequence, the research emphasis in developing new analgesics has shifted from opioid receptors to a plethora of newly discovered targets [115]. Compounds active at these sites are either still in the early stages of preclinical development, have yet to show robust clinical effects, have unexpected side effects or are inactive in humans, *e.g.*, NK1 receptor antagonists [34].

The difficulty associated with developing new analgesics reflects the complex neurobiology underlying its transmission and perception, and the difficulty in recapitulating the human condition in animal models. An example of the latter is the fact that chronic pain in rodents, such as that associated with a neuropathy, is established and measured in weeks rather than the years typically encountered in the clinical setting [115,116]. The expectation that selective cyclooxygenase-2 (COX-2) inhibitors would be more effective and safer than aspirin and related agents was dashed with the discovery that these drugs may be associated with an increased incidence of myocardial infarctions and ischemic strokes. This finding ultimately led to the withdrawal from the market of rofecoxib and valdecoxib despite their efficacy in arthritic patients [117].

2.5. *Anti-inflammatory agents and immunopharmacology*

A range of new therapies has been developed in recent decades for treating inflammation and chronic inflammatory diseases including asthma, Crohn's disease, rheumatoid arthritis (RA), psoriasis and lupus erythematosous. Nonetheless, the number of such drugs remains small and all display side effects that limit their use. A prime example is the COX-2 inhibitors that, although more selective than classical nonsteroidal anti-inflammatory drugs (NSAIDs), display ulcerogenic effects and, at sustained high doses, increase the risk of heart disease and stroke [117,118]. Despite some complications, anti-TNF therapy remains efficacious [119]. Anti-TNF monoclonal antibodies, including infliximab, adalumumab and certolizumab-pegol, benefit patients with RA or psoriasis [120]. Rituximab, which targets CD20 on B cells [121], and abatacept, which disrupts the interaction between dendritic and T cells, are newer RA treatments [122]. Side effects encountered with many of these therapies are likely due to inhibition of endogenous factors that play an important role in normal physiology or to effects on innate immunity. There thus remains a large unmet medical need. A better understanding of the cellular and molecular mechanisms of inflammation based on biochemical approaches has yielded newer targets [123,124] including members of the canonical inflammatory transduction pathway activated by TNF, IL-1, TCR, BCR and the TLRs and NLRs that culminate in NF-kB and activation of the IKK complex. AS602868, an IKK2 inhibitor, has shown promise in treating multiple myeloma [125]. MAP kinases are also promising targets, especially the p38 and JNK pathways. Several p38 inhibitors are active in the treatment of RA, Crohn's disease and psoriasis [126]. Moreover, the characterization of the TCR pathway has contributed to the development of several agents, such as FK506 and cyclosporine, that inhibit calcineurin, a calcium-dependent phosphatase [127].

3. Selectivity, side effects and off target actions

In vitro assays, such as screening techniques, are simple ways to assess the target potency and selectivity of NCEs [128]. *In vitro* assays are also useful for evaluating metabolic stability prior to advancing compounds to analysis using more costly and time consuming intact tissue and whole animal tests. Many of these biochemical assays can be performed in high throughput mode [129,130], resulting in the generation of enormous amounts of data. Both academia [131], through the U.S. National Institute of Mental Health (NIMH) Psychoactive Drug Screening Program [128], and industrial scientists, through work conducted at contract laboratories [132], routinely obtain screening data from analyses at 400 or more of the molecular targets known to be involved in drug actions or side effects. Most publications on NCEs advancing to the clinic now contain such screening data and these results are typically included in Investigational New Drug applications to provide a broader understanding of potential NCE interactions. The conceptual value of high throughput assays has also been extended to pathway-based approaches to better understand drug actions, to develop possible biomarkers [133], and to analyze the behavioral effects of compounds via testing batteries Psychogenics' SmartCube™ [134,135], that compliments the phenomenon of ''targophilia''.

4. The next 50 years of biochemical pharmacology

The impact of biochemical pharmacology on furthering the understanding of human disease and its treatment is readily apparent even to a casual observer. The question remains as to

how biochemical pharmacology will contribute to these objectives over the next 50 years.

The NIH Pathway Initiative [38] on translational research has been complimented by white papers from the U.S. Food and Drug Administration (FDA) and the U.S. Government Accounting Office, the 'Critical Path Initiative' [136], and New Drug Development [137], respectively, that address the poor rate of drug discovery in recent years and its impact on human health. Additionally, the NIMH has instituted programs to foster collaboration between industry, academia and government laboratories [112,138].

The FDA's 2004 white paper [136] noted an urgent need to "strengthen and rebuild the disciplines of physiology, pharmacology and clinical pharmacology", a view that had been expressed a decade earlier by a prominent group of pharmacologists [139]. Unfortunately, in the ensuing decade, pharmacology training was given little priority as funding agencies increased the emphasis on underwriting studies in molecular biology [140]. This inevitably led to a shortage of pharmacologists and of biomedical scientists without any exposure to basic principles of pharmacology, such as the need to generate dose–response curves [141] and the ability to critically plan, analyze and interpret such data. Attempts are being made to rectify this situation by initiatives such as the NIH-sponsored Integrative and Organ Systems Pharmacology (IOSP) courses [142], 2–3 week long workshops at universities in the U.S. There are similar training programs in Europe [143]. While the focus is primarily on familiarizing biomedical scientists with assays conducted in whole tissue and animal models, the material is organized around a solid understand of receptor theory [8].

In terms of where the discipline of biochemical pharmacology will be in 2058, newer approaches to modify cellular and tissue function, such as RNA interference [144] and stem cell replacement [145], remain to be proven as viable alternatives to drug therapy. Indeed, because of its hypothesis driven nature, pharmacology offers the antidote to Horrobin's legitimate concern that biomedical research has "taken a wrong turn in [its] relationship to human disease" [146]. As for *Biochemical Pharmacology*, its original purpose as expressed by Haddow [2] to "... encourage and record ... [the] spectacular progress [that] has occurred ... in many ... branches of cellular pharmacology" remains the goal of the current editorial team. Efforts will continue to keep *Biochemical Pharmacology* rated among the best of its peers in attaining this objective.

Note added in proof

The reader is also referred to the excellent review on great discoveries in pharmacology by Rubin [147] written as part of the ASPET Centennial.

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