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Pharmacy Education: The Driving Force for Change, Stature and Influence of Our Profession

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As we celebrate 100 years of Pharmacy Education at the NDMC, I have been a part of Pharmacy education for 53 years, and my family for >75 years. There is no doubt that the changes in the profession that have occurred over these last 100 years have almost all been generated and driven by cutting edge changes in the educational process. Influence and stature of a discipline comes about when that discipline offers a needed service or intellectual advancement that is not found within other disciplines. Pharmacy and Pharmacy education over the years have searched for the key component that would make our discipline/profession not only unique, but derive influence and stature. We have advanced along many avenues during our search: compounding, manufacturing, medicinal chemistry, pharmacognosy and natural product chemistry, physical pharmacy, drug delivery, clinical and patient oriented pharmacy practice, clinical pharmacology, pharmacoeconomics, pharmacoepidemiology, nanotechnology, drug metabolism/transport and personalized medicine. However, I will concentrate on what I believe to be an advancement that occurred through Pharmacy education, almost exclusively, which has had the largest impact. That advancement is the invention and development of clearance concepts. In my mind, clearance is the vehicle that provided the sound basis for our disciplines' unique rolls in clinical and patient oriented practice, drug metabolism/transport and personalized medicine. It is a parameter that medicinal chemists and drug delivery scientists take into consideration in their new advances and it is the basis for the pharmacist, in essence, assuming the roll of clinical pharmacology in patient care.

Key Words: pharmacy education, clearance concepts, pharmacokinetics, personalized medicine

INTRODUCTION

It is my great pleasure to present a Keynote Speech at the 100th Anniversary of the School of Pharmacy, NDMC and to provide this written report. This is my fifth visit to Taiwan, the first being in 1975 where I presented lectures at the NDMC School of Pharmacy and Tri-Service General Hospital. My subsequent visits were in 1989, 1997 and 2000. I have had outstanding interactions with the faculty and students of the School of Pharmacy, NDMC and am very proud of my friendships with the faculty and students here over the years.

I note that the 100th Anniversary of the School of Pharmacy NDMC corresponds to the 100th Anniversary of Awarding the Nobel Prize to Dr. Paul Ehrlich. Ehrlich is given credit for initiating chemotherapy and the "magic bullet" concept with his discovery of Salvarsan for the treatment of syphilis. In October 2008, I spoke at the second World Congress on Magic Bullets Celebrating the 100th Anniversary of awarding the Nobel Prize to Paul Ehrlich and it appropriately served as a basis for reviewing the pharmaceutical disciplines that existed at that time coincident with the founding of the NDMC School of Pharmacy. Those disciplines included medicinal chemistry, pharmacognosy, materia medica and Galenics with a focus on compendial standards. Twelve years from now we will celebrate the 200th Anniversary of the establishment of the first drug compendia, the United States Pharmacopeia (USP). These standards were recognized by a governmental agency in 1906 in the U.S. through the Pure Food and Drug Act.

It is important to consider the history of regulatory issues in discussing pharmacy and pharmacy education. Table 1 lists a number of important FDA milestones. Although the original Food and Drug Act in 1906 recognized the USP as a regulatory standard, the Agency had very little power and the Act was primarily related to

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Table 1 Important FDA Milestones

- 1906 Original Food and Drug Act
- 1931 FDA Formed
- 1938 FD&C Act (Drugs had to be safe)
- 1951 Durham-Humphrey Amendment (Rx)
- 1956 Kefauver-Harris Drug Amendments (Drugs had to be effective)
- 1984 Hatch-Waxman Drug Price Competition and Patent Term Restoration Act (Generic Drugs)

curbing narcotic abuse in home remedies and standards of cleanliness in the meat packing industry. The FDA was formed in 1931 in the U.S. as the first governmental food and drug regulatory agency, but the Agency had very little authority in terms of regulating drugs and drug products. This came about in 1938 through the Food Drug and Cosmetic Act, which resulted from Congressional and public concern with the death of 107 children due to ingestion of Sulfanilamide Elixir, which used diethylene glycol as a solvent. Of course, we all know that in the body diethylene glycol breaks down to ethylene glycol, the poisonous antifreeze used in automobiles. It is interesting to note that the company that manufactured the Sulfanilamide Elixir was only guilty of violating USP standards, since by definition the use of the term elixir required 10% ethanol to be in the product. The company paid a fine for this violation but had no further liability related to the deaths of these 107 children. As a result of this incident, however, passage of the FD&C Act in 1938 required that drugs be safe and gave the FDA the authority to assure that this regulation be met.

Another key FDA regulation of particular interest to pharmacy was the 1951 Durham-Humphrey Amendment that required drug products to be dispensed in the United States on the receipt of a prescription. I note that Hubert Humphrey, one of the authors of the bill, later became Vice President of the United States and ran for President. In the U.S. Hubert Humphrey is the only President or Vice President (elected or a candidate) who was a health professional. Hubert Humphrey was a pharmacist, and of particular interest to my family. Mr. Humphrey was a classmate of my father at the Capitol College of Pharmacy in Denver, Colorado, an institution that no longer exists.

Until 1956 there was no regulatory requirement that drugs had to be effective, only that they be safe. This was changed by the Kefauver-Harris Drug Amendments that were initiated by the public outcry related to the teratogenicity resulting from thalidomide, which in the late 50s and early 60s was prescribed as an anti-emetic to combat morning sickness in pregnant women, but which resulted in phocomelia [short or absent long bones and flipper like appearance of hands and feet]. The Kefauver-Harris Drug Amendments required that drugs not only be safe, but that they also had to be effective.

Finally, of particular relevance to pharmacy is the 1984 Hatch-Waxman Drug Price Competition and Patent Term Restoration Act, which served as the basis for the rules utilized today in regulatory agencies throughout the world for the approval of generic drugs. This occurs through an abbreviated new drug application that does not require safety and efficacy studies, but rather makes approval contingent upon non-significant changes in the rate and extent of bioavailability through measurements of systemic drug concentrations.

It is my belief that the imposition of regulatory standards to assure the safety and efficacy of drug products, although mandating a role for pharmacy and the pharmacists in drug therapy was a driving force to decrease the influence and importance of the pharmacist as a leader in therapeutics. This emphasis of pharmacy practice on the drug product rather than patient care has been reversed today as I will detail below.

BENET FAMILY PHARMACY HISTORY

In preparing for this presentation, I reflected upon my own family history over the past 100 years corresponding to the NDMC School of Pharmacy history. In 1908, my father Jonas and my uncle Harry Benet were 6 and 9 years old, respectively. As young children they worked as delivery boys for the local pharmacy and decided to pursue the pharmacy profession. My uncle Harry graduated as a pharmacist from the University of Kentucky and my father, as noted above, from the Capitol College of Pharmacy in Denver. They received Ph.G. degrees, i.e. graduate pharmacist. They opened Benet's Pharmacies in Cincinnati, Ohio in the 1930s that almost exclusively dispensed prescription drugs, and specialized in products that they manufactured. It was depression years throughout the world, but in the United States it was also the time of temperance laws. As pharmacy owners and manufacturers they had the right to prepare and dispense alcohol for "medicinal purposes". In the 1940s they founded DARA Products, the first drug company to make hypoallergenic dermatologicals. One of their secrets was changing the pH of the preparations

to 7.4, which made the shampoo amphoteric and sold as a "soapless" shampoo.

The family plan was for me to go to pharmacy school, then get a graduate degree and come home and run the company. Therefore, I enrolled in the College of Pharmacy at the University of Michigan in 1955. Looking back today, I recognize that the curriculum that I followed, differed little from the curriculum discussed above from the early 1900s. My courses included Pharmacy Calculations, Compendial Standards, Pharmacognosy, Medicinal Chemistry, Pharmaceutical Analysis and a new course substituting for Galenics called Physical Pharmacy. I also took courses in Physiology and Pharmacology, but now that I think back there was surprisingly little emphasis on biological subjects during my pharmacy training. And of course, I took the "Capstone" course Dispensing.

But I didn't view pharmacy in the late 1950s as a profession that had significant stature and influence. Most of the basic sciences disciplines in the field, except for pharmacognosy, were "me-too" fields, where the major advances were being made in the historical non-pharmacy basic science or medical school departments. I was particularly intrigued with the mathematical and physical chemistry basis of the courses in physical pharmacy, so I decided to go to graduate school in this discipline. My family was happy because they thought this was the closest field to coming back to run DARA products, and I didn't let them know then that my goal was Academia. In 1960 I entered the Pharmaceutical Chemistry Graduate Program at the University of Michigan working under Professor Jere Goyan (who later served as Dean of the UCSF School of Pharmacy and FDA Comissioner) deriving basic principles for the dissociation of multivalent acids and investigating the thermodynamics of chelation of tetracyclines. I took many advanced math and physical chemistry courses, chemical engineering unit operations but no biology and pharmacology courses. Dr. Goyan was recruited to UCSF at the end of my third year and I accompanied him. I chose to take my degree from UCSF and then was required to re-take my qualifying exams, including pharmacology at UCSF, adding another year to my graduate program.

Upon graduation I chose not to do a postdoc, since I had two academic job offers and I was recruited to Washington State University to teach physical pharmacy and pharmaceutical analytical chemistry. I discovered that what I knew about pH may be useful in understanding drug absorption and my first NIH grant was funded nine months after I joined the WSU faculty. From afar I was amused at the mathematical naïveté of a new field, pharmacokinetics. Then after four years I was recruited back to UCSF to teach physical pharmacy, since no one thought I knew any biology.

THE PHARMACY CURRICULUM 40 YEARS AGO

In reviewing the pharmacy curriculum at Washington State University and UCSF forty years ago, I am struck that not much had changed since I studied pharmacy at the University of Michigan 10 years earlier. Dispensing was still the "Capstone" course and all the courses, except for compendial standards, were still in the curriculum, although the emphasis on biology (physiology/pharmacology + pathology) had increased. But a number of faculty members at UCSF (primarily those with physical pharmacy graduate training) believed that the knowledge and skills of pharmacy graduates were not being fully utilized and these faculty began to push for patient oriented training versus product oriented training. The first clinical pharmacist support to medicine was initiated as the 9th Floor Project at UCSF and a clinical pharmacy curriculum began to evolve in the 1960s.

Yet, there was strong opposition to this new role for pharmacists from both physicians (as I recall most vehemently from pharmacists who had gone on to get a medical degree) and from pharmacists, particularly industrial pharmacists who couldn't believe that anyone would be willing to pay for such clinical pharmacy expertise. And, although the role of the pharmacist in patient care began to grow, I frequently heard the comment that a medical specialist in a particular field still had more knowledge of therapeutics in that patient population than the clinical pharmacist.

WHAT WAS MISSING?

With the evolution of the Clinical Pharmacy Program there was still something missing. There was no unique and significant contribution that the pharmacist could bring to patient care that would not be within the expertise and training of other health professionals. This missing component had to be a discipline that was not "me-too" science taught with a specialized emphasis in the pharmacy curriculum and which was not found in other health science curricula. What began to evolve, again from those trained in physical pharmacy, was the nascent field of pharmacokinetics.

However, the mathematical emphasis and the premise of pharmacokinetics were unintelligible both to physicians and pharmacists in its initial conception.

Reviewing the pharmacokinetic literature forty years ago almost all published studies were carried out with salicylic acid. This was because the drug was given in large doses, and primarily because we had a colorometric assay, using the Bratton Marshall reaction, that allowed us to measure plasma and urinary concentrations. However, the mathematical models that were developed and the equations that accompanied these models although of interest to the cognoscente were incomprehensible to clinicians treating patients. Furthermore, there appeared to be no useful relationship between the changes in these pharmacokinetic parameters and the degree of disease, which would allow translation of pharmacokinetics to patient drug dosing.

So in 1972 what was wrong with pharmacokinetics? It appeared to have no relationship with clinically meaningful parameters that could help in making drug dosing decisions or that could account for differences in physiology and pathology. For example at steady state:

Rate In = Rate Out

Availability x Dosing Rate= ?? x Average Concentration

F x Dosing Rate = ?? x Target Concentration

It was well known that at steady state the Rate In would be the dosing rate at which the drug was administered multiplied by the bioavailability (F), which could change as a function of the route of administration. It was recognized that Rate Out should relate to these systemic concentrations or to a target concentration that was known to yield efficacy with minimum toxicity. However, the parameter that was to be multiplied by this systemic target concentration was undefined in 1972. Therefore, we invented it and called it clearance (CL). So that at steady state:

Rate In = Rate Out

Availability•Dosing Rate = Clearance•Concentration at steady-state

$$F * Dose/\tau = CL * C_{ss} \qquad \text{(Eq. 1)}$$

where τ is the dosing interval and C_{ss} is the concentration at steady state. From the equality in Eq. 1 it can be determined that the units of clearance are flow parameters or volume per time.

A number of experimental observations in the late 1960s, early 1970s could not be explained by the pharmacokinetic theory available at that time. For example von Bahr et al.[1] observed that for rats receiving phenobarbital as an enzyme inducing agent the elimination of phenylbutazone was increased both in vitro in liver microsomes and in vivo in whole animals versus that observed in non-induced animals. However, for the drug desipramine, although elimination was increased in microsomes from phenobarbital induced rats, no change in plasma disappearance was noted in vivo for this drug between rats induced with phenobarbital and control rats. Another series of studies related to protein binding also showed discontinuities for certain drugs between in vitro and in vivo studies. Krüger-Thiemer and colleagues[2] showed that inhibition of protein binding would increase free concentrations of a large number of sulfa drugs. They reasoned, therefore, that in vivo they would expect the renal elimination of these sulfa drugs to increase when protein binding was inhibited. For some sulfa drugs this in vivo increase in renal elimination was observed, however, for a number of sulfas no change in renal elimination was found when free concentrations of the drugs were increased by inhibiting protein binding. Thus it appeared in the early 1970s that pharmacokinetics did not provide any predictability of changes in elimination based on induction of metabolic enzymes or through increasing free drug concentrations.

However, the introduction of clearance concepts in pharmacokinetics by Rowland, Benet and Graham in 1973[3] and the further explication by Wilkinson and Shand in 1975[4] alleviated these problems. Rate of elimination for an individual organ can be defined as the blood flow to that organ (Q) and the difference between the arterial C_A and venous (C_V) concentrations as shown below:

$$\text{Rate of elimination} = Q \cdot C_A - Q \cdot C_V$$

From Eq. 1, organ clearance equals the rate of elimination divided by the concentration as shown in Eq. 2, where the difference in arterial and venous concentrations divided by the incoming arterial concentration may be defined as the extraction ratio (ER) of the organ.

$$CL_{organ} = (Q \cdot C_A - Q \cdot C_V) / C_A$$
$$= Q \cdot (C_A - C_V) / C_A = Q \cdot ER \qquad \text{(Eq. 2)}$$

However, Eq. 2 would not explain the anomalies listed above. Thus the development of clearance in pharmacokinetics[3,4] was advanced by describing the extraction ratio in terms of the "well-stirred" model that we borrowed from the chemical engineers as used by

them in modeling the "cracking" of petroleum to make gasoline. We define extraction ratio as a function of three parameters:

a. blood flow to the elimination organ
b. the fraction of drug unbound in the blood, and
c. the intrinsic ability of the organ to eliminate the unbound drug if there were no flow and protein binding limitations.

In terms of the well stirred model, clearance (with respect to blood concentrations) for the eliminating organ then becomes:

$$CL_{organ} = Q \cdot (fu_b \cdot CL_{int}) / (Q + fu_b \cdot CL_{int}) \qquad \text{(Eq. 3)}$$

where fu_b is the unbound fraction of drug in blood. Equation 3 demonstrates that when the capability of the eliminating organ to metabolize the drug is large in comparison to the rate of drug presentation to the organ, i.e., $fu_b \cdot CL_{int}$ is much greater than Q, the clearance will approximate the organ blood flow

$$CL_{organ} \cong Q \qquad \text{(Eq. 4)}$$

That is, drug elimination is limited by blood flow rate and the compound is called a high-extration-ratio drug. On the other hand, when the metabolic capacity is small in comparison to the rate of drug presentation ($Q >> fu_b \cdot CL_{int}$), the clearance will be proportionate to the unbound fraction of drug in blood and the intrinsic clearance, as in Eq. 5.

$$CL_{organ} \cong fu_b \cdot CL_{int} \qquad \text{(Eq. 5)}$$

The drug is then called a low-extraction-ratio drug. When the capability for elimination is of the same order of magnitude as the blood flow, clearance is dependant upon the blood flow as well as on the intrinsic clearance and the plasma protein binding (Eq. 3).

Note that the definitions for low- and high-extraction-ratio drugs are independent of the fraction of the dose eliminated by a particular organ. For example, diazepam is eliminated almost completely by hepatic metabolism (less than 1% of the drug is excreted unchanged in the urine), yet the clearance of diazepam, 27mL/min, indicates that this is a low hepatic extraction ratio. That is, on each pass through the liver only a small fraction of the drug ($ER_H = 27/1{,}500 = 0.018$) will be eliminated, although eventually almost all of the drug will be eliminated by the liver. The value of 1,500 is the average hepatic blood flow in mL/min for a 70kg man.

Equation 3 clarifies a number of the unresolvable experimental results described above. For example, enzyme induction or hepatic disease may change the rate of desipramine metabolism in a hepatic microsomal enzyme system, but no change in clearance is found in the whole animal with similar hepatic changes. This is explained by the fact that desipramine is a high-extraction-ratio drug and clearance becomes limited by blood flow rate (Eq. 4), so that changes in CL_{int} due to enzyme induction or liver disease have little effect on clearance. Also, although desipramine is a relatively highly protein bound drug ($fu_b = 0.18$), changes in protein binding due to disease or competitive binding should have little effect on clearance. In contrast, for a low-extraction-ratio drug such as phenylbutazone (CL = 1.6mL/min/70kg), enzyme induction or changes in protein binding ($fu_b = 0.039$) should markedly affect elimination since Eq. 5 describes this drug's elimination.

The introduction[3] of clearance concepts to pharmacokinetics beginning in 1973 has had an immense effect on the field. Reviewing PubMed for the term "drug clearance" one finds in 1972 that there were 192 references, many of them dealing with mucociliary drug clearance. In the year 2006 the total number of references increased to more than 29,000 and as of the end of 2008 the number of references is greater than 46,000. Thus beginning in 1973 it was recognized that clearance, not half-life, was a measure of the body's ability to eliminate drug and changes in pathology or physiology could be correlated with measures of clearance.

This initially created some confusion because up to that time half life was well recognized in terms of basic chemical principles as an appropriate measure of the rate of elimination and reflective of changes in the rate of elimination. However, the difference between chemistry and pharmacokinetics is that in chemistry the volume in which the reaction occurs does not change. In contrast, in pharmacokinetics, disease states and differences in physiology can change the space available in which the drug may distribute in the body. Thus, it was necessary to develop a measure of volume of distribution that was independent of elimination. Such a volume term had been defined as volume of distribution at steady state (V_{ss}). Although clearance could be determined independent of the previously employed pharmacokinetic models by determining dose divided by the area under the curve (AUC), no noncomparatmental method for determining V_{ss} was available until 1979. Then Benet and Galeazzi[5] defined a noncompartmental method for determination of V_{ss} . This paper was the first to describe the relationship between V_{ss} , CL and a measure of time of drug in the body, the mean residence time (MRT).

$$V_{ss} = CL \cdot MRT \qquad \text{(Eq. 6)}$$

(This is my most frequently cited publication, and in fact, the highest cited paper in the Journal of Pharmaceutical Sciences.) Now it was recognized that clearance and volume were the independent parameters and that half life or MRT (a measure of inverse half life) was the dependent parameter. Changes in either clearance or volume could change half life.

A major impetus to the recognition of the importance of pharmacokinetics in drug development and therapeutics was the invitation to prepare a table of pharmacokinetic data for the 1986 edition of Goodman and Gilman has been shown in Table 2. In the following edition, Dr. Sheiner and I were invited to prepare the first chapter and to present for the first time clearance concepts to the general medical community. I am very happy to have been invited again to participate in preparation of this first chapter in the 2010 12th edition.

Table 2 The early history of pharmacokinetics in Goodman and Gilman

Edition	Year	Number of Drugs	Authors
6th	1980	98	L.Z. Benet and L.B. Sheiner
7th	1985	188	L.Z. Benet and L.B. Sheiner
8th	1990	243	L.Z. Benet and R.L. Williams
9th	1996	334	L.Z. Benet, S. Øie & J.B. Schwartz

Chapter 1 Pharmacokinetics: The Dynamics of Drug Absorption, Distribution and Elimination

7th	1985	L.Z. Benet and L.B. Sheiner
8th	1990	L.Z. Benet, Jerry R. Mitchell & L.B. Sheiner
9th	1996	L.Z. Benet, D.L. Kroetz & L.B. Sheiner
12th	2010	I.L.O. Buxton & L.Z. Benet

Goodman and Gilman's
The Pharmacological Basis of Therapeutics Appendix II Design and Optimization of Dosage Regimens: Pharmacokinetic Data

Clearance concepts and academic pharmacy not only influenced the profession in terms of patient care, it also had a marked influence on the FDA and the drug development process. Clearance is now the parameter that medicinal chemists and drug delivery scientists take into consideration in their new advances with the recognition that exposure of drug in the systemic circulation is the driver that will lead to a drug or a delivery vehicle being commercialized.

In 1977 we formed, within UCSF, the first academic contract research organization in the U.S., the "Drug Studies Unit". In fact, the DSU was among the first clinical CROs, even including the for-profits. We established clinical, bioanalytical and data analysis sections of the DSU. Our objective was to carry out high quality Clinical Pharmacology/Pharmacokinetic studies for the industry that would improve the drug development process. We felt that the DSU was an important contributor to the recognition that academic pharmacy could have a marked impact in drug development. In fact, we invented a new dosage combination for triamterene and hydrochlorothiazide and this became a commercial success under the trade name Maxide®. All of the pharmacokinetic development was carried out at UCSF[6,7] and we also designed and supervised the multi-center clinical studies necessary for clinical approval. The Drug Studies Unit also played an instrumental role in the commercialization of metformin. All of the early Phase 1 and Phase 2 studies were carried out by the DSU[8-10].

WHERE ARE WE TODAY ?

Pharmacokinetics and clearance concepts, as well as their application to patient care were also a major focus of a new medical discipline in the 1970s, Clinical Pharmacology. The medical disciplines of Clinical Pharmacology and Infectious Diseases (ID) began in parallel at that time. But today although ID has flourished and grown tremendously as a patient care and research discipline, Clinical Pharmacology in medicine has become only a research discipline, primarily because the patient care aspects of the field have flourished and grown in Pharmacy, and every patient can benefit from the field. It is my contention that the evolution and understanding of clearance and its use in therapeutics and drug development was the essential contribution that was unique to pharmacy and served as a differentiating contribution for our profession. Personalized medicine, individualization of drug dosing based on genetic characteristics had its basis in clinical pharmacy. I believe that the breakthrough of the specialized and unique discipline to pharmacy and its translation into patient care has ameliorated the perception of other academic pharmacy disciplines as "me too" sciences. And it is now well recognized that pharmaceutical sciences and all of our disciplines have exceptional capability. This has also been helped by the pharmaceutical science organizations

functioning independent of the profession.

For example, in 1986 when the American Association of Pharmaceutical Scientists was formed, primarily through the leadership of academic pharmacy school faculty, some bemoaned this as a negative for the profession of pharmacy. However, AAPS with its more than 13,000 members, versus the approximately 2,000 scientist member of the old APhA Academy of Pharmaceutical Sciences in 1985, has given stature and influence to the academic pharmacy disciplines far beyond that which could be obtained as a subset of the profession.

In summary, academic pharmacy has advanced along many avenues during our search: compounding, manufacturing, medicinal chemistry, pharmacognoscy and natural product chemistry, physical pharmacy, drug delivery, clinical and patient oriented pharmacy practice, clinical pharmacology, pharmacoeconomics, pharmacoepidemiology, nano technology, drug metabolism/transport and personalized medicine. Our future is very bright, as we are recognized as being composed of disciplines that have much to offer. Once again it is my honor to be invited to present my thoughts on this significant anniversary for pharmacy education at NDMC. Congratulations to the school, its faculty and students as you move forward in the next 100 years.

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