



## Clinical Pharmacy in the Genomic Era

**Title in Spanish:** *Farmacia clínica en la era del genoma*

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**ABSTRACT:** Over a century ago Gregor Mendel investigated quantitatively how physical traits of plants were passed on from one generation to the next. Soon after, William Bateson and Archibald Garrod showed the relevance of Mendel's findings to human disease. Pharmacists have throughout history marketed themselves as experts who could treat disease with specific medicines. Their claims were however poorly validated until Louis Pasteur and Robert Koch established the microbial aetiology of many diseases. Effective antimicrobial agents and immunotherapies soon became available for an expanding range of infections, and personalisation of treatment became possible through sensitivity testing. Later, a greater understanding of the molecular pathogenesis of non-microbial diseases led to the development of effective drugs, such as antihypertensives and anticoagulants. As a result, current pharmacopoeias bear no resemblance to their predecessors cluttered with predominantly useless drugs. With the unravelling of the double helical structure of DNA and greater understanding of its implications for health and disease, pharmacopoeias are being rewritten again. The new drugs enable an unprecedented level of individualisation of therapy. To optimise the promise of these drugs, input from a new generation of well-informed clinical pharmacists is needed. In this presentation, we identify some of these developments, and where input from pharmacists is most likely to be required. Will clinical pharmacists deliver?

**RESUMEN:** Hace más de un siglo Gregor Mendel investigó cuantitativamente cómo se transmitían los rasgos físicos de las plantas de una generación a la siguiente. Poco después, William Bateson y Archibald Garrod mostraron la relevancia de los hallazgos de Mendel en las enfermedades humanas. A lo largo de la historia, los farmacéuticos se han considerado como expertos que podían tratar la enfermedad con medicamentos específicos. Sin embargo, sus afirmaciones fueron mal validadas hasta que Louis Pasteur y Robert Koch establecieron la etiología microbiana de muchas enfermedades. Los agentes antimicrobianos eficaces y las inmunoterapias pronto estuvieron disponibles para un número de infecciones en expansión y la personalización del tratamiento se hizo posible a través de pruebas de sensibilidad. Posteriormente, una mayor comprensión de la patogénesis molecular de las enfermedades no microbianas condujo al desarrollo de fármacos eficaces, tales como antihipertensivos y anticoagulantes. Como resultado, las farmacopeas actuales no guardan ningún parecido con sus predecesoras llenas de drogas básicamente inútiles. Con la desintegración de la doble estructura helicoidal del ADN y una mayor comprensión de sus implicaciones para la salud y la enfermedad, las farmacopeas se están volviendo a escribir. Los nuevos fármacos permiten un nivel sin precedentes de individualización de la terapia. Para optimizar la promesa de estos fármacos, se necesita el aporte de una nueva generación de farmacéuticos clínicos bien informados. En esta presentación, identificamos algunos de estos desarrollos y el lugar en el que el papel de los farmacéuticos es más probable que sea necesario. ¿Cumplirán los farmacéuticos clínicos?

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### INTRODUCTION

I would like firstly to thank the President, Professor Mariano Esteban Rodriguez, and members of the Royal National Academy of Pharmacy, Instituto de España, for offering me the great honour of foreign membership. I am of course very thankful to Professor Alfonso Dominguez-

Gil for presenting my candidacy to your Academy. It is also with immense pleasure that I thank my great friend of many years, Professor Francisco Javier Burguillo for nominating me.

Historical accounts of the development of medicines often start with the Egyptian Ebers papyrus, the

application of the doctrine of signatures in Europe, or the pharmacopoeia of the Chinese Yellow Emperor. For this lecture, delivered in the grand city of Madrid at the kind invitation of the Spanish Royal Academy of Pharmaceutical Sciences, I would like to begin here. For it was the Jesuit Cardinal Juan de Lugo, a Madrilenian, trained at your famous University of Salamanca, only a few miles from here, who brought the first truly effective medicine, the first 'miracle' drug, to the attention of the old world while serving as the Director of the apothecary at the Santo Spirito Hospital in Rome. That medicine, the cinchona bark or quinine, has saved countless lives since those mid-seventeenth century days when Father Bartholmé Tafur, the Peruvian Jesuit brought a small stock from San Pablo for his Jesuit superior. As demand grew, a Spanish Royal Order was issued in 1751 for the establishment of a Royal monopoly for trading cinchona bark, with supplies located in the Royal Pharmacy here in Madrid.

There would not be another miracle medicine until the late nineteenth century although the therapeutic value of opium had been discovered centuries earlier, both in the East and West, and morphine was isolated as a pure medicinal chemical by Friedrich Sertürner in 1804 (1).

The age of modern synthetic medicines is perhaps best anchored to the late 19<sup>th</sup> century with heroin and aspirin, both derivatives of naturally-occurring molecules; morphine and salicin (the salicylic acid glucoside prodrug) respectively. However, compared to the next revolution, brought about by the Pasteur's and Koch's discovery and proof of the microbial basis of many of the most devastating diseases, those advances were modest in terms of lives saved though not necessarily of pain avoided.

### THE BIRTH OF MODERN PERSONALISED MEDICINE

The medical and pharmaceutical professions have always claimed that their clinical practice was

personalised; the doctors that their diagnoses were specific and the pharmacists that their medicines were specifics. The emptiness of those claims have resonated down the centuries. Pasteur and Koch, and later Paul Ehrlich and Emil von Behring, established the methodology for validating such claims using the microscope and specific stains, and Behring's serum therapy against diphtheria was the first truly effective antibody therapy. Jenner had earlier, of course, developed the first vaccine which eventually eliminated smallpox worldwide on an empirical basis before the cause was identified.

### VARIABILITY IN HUMAN RESPONSE

One of the great puzzles for the early non-charlatan physicians was the wide variability in their patients' responses to medicines. With the benefit of hindsight, some of the reasons are obvious: (i) natural variability in the chemical composition of plants (e.g. the variable pungency of Spanish chilies even of the same variety, and variation in the quality of wine, give some clear clues), (ii) misdiagnosis (e.g. of fevers), (iii) adulteration, deliberate or through ignorance, and (iv) variable dosing.

Paracelsus (2) knew of the importance of dosing, stating, 'All substances are poisons ... The right dose differentiates a poison and a remedy.' Arthur Koestler, the colourful writer, once imprisoned in Seville during the tumultuous period of your National history, knew after he failed in a suicide attempt. 'Trying to commit suicide is a gamble the outcome of which will be known to the gambler only if the attempt fails, but not if it succeeds,' he said when he tried again years later. Sadly, the dose and drug combination he chose did work that time, both for him and his wife in their double suicides.

If drug response is so variable, then it is obvious that personalizing their use would potentially improve therapy (Figure 1).

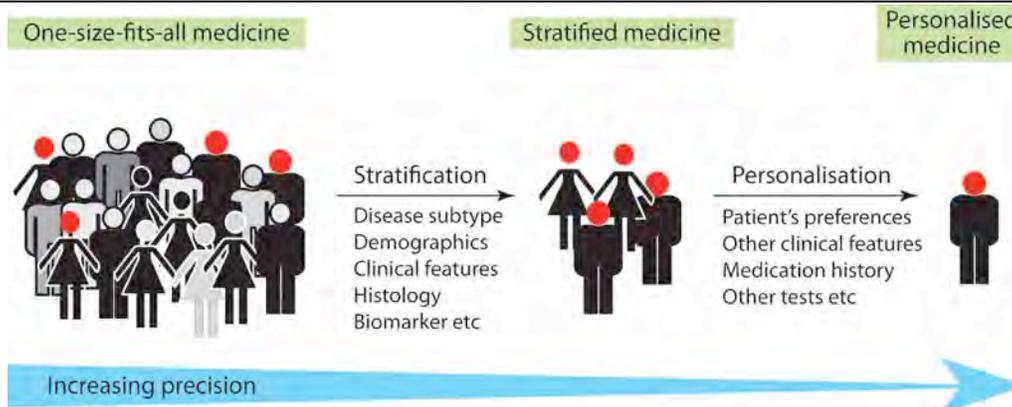


Figure 1 From one-size-fits-all to personalized therapy.

### THE BIRTH OF PHARMACOGENETICS

Pharmacogenetics can be defined as the study of the impact of genetic variation on response to biologically active substances (pharmacocons). More generally, the term pharmacogenetics can be enlarged by substituting 'genetic

variation' with 'inheritance.' This extension is important as we inherit not only our genes from our parents but also our microbiome and our cultures, including our diet and our preferences, all of which may affect the action of the drugs we take.

Folklore ascribes the birth of pharmacogenetics to Pythagoras (3), the 6<sup>th</sup> to 5<sup>th</sup> century BC Greek philosopher, mathematician, and mystic because he forbade the eating of broad beans which causes haemolysis in some susceptible subjects. This causal association which was subsequently linked to an inborn deficiency in glucose-6-phosphate dehydrogenase (G6PD) established him as the first pharmacogeneticist in the eyes of many.

Over two millennia later, the perceptive Charles Darwin recognised that adaptation contributed to wide variability in people's responses to toxins and that through natural selection different groups could develop different levels of resistance to toxins at the population level. However, Darwin found it difficult to provide a mechanism for inheritance. He theorized that when children are conceived, they inherit a blend of their parents' traits. Black and white would yield in-between shades of grey. He was unable to explain why blending did not continue until there was no more white or black.

The theory of numbers developed by Pythagoras and his followers would help resolve Darwin's dilemma. The sciences of numbers, they said, could be divided into two broad classes: numbers to describe how many (discrete mathematics) and numbers to describe how much (continuous mathematics). Pythagoras used continuous mathematics to describe music, and thereby also laid the foundation of harmonics.

It was with the use of discrete mathematics that Gregor Mendel generated the data for his Laws of Inheritance with his studies of the genetics of peas.

The discovery of monogenic diseases

Darwin was not aware of Mendel's work. In fact, even Mendel's contemporaries working on plant breeding did not immediately recognise the significance of Mendel's work. However, one biologist, William Bateson, working in Cambridge, soon recognised the wider significance of Mendel's discoveries.

Archibald Garrod, an astute London clinician inferred that alkaptonuria, a strange and rare condition characterised by the deep browning, and eventual blackening of urine, when exposed to air, was due to a metabolic abnormality that led to the accumulation of homogentisic acid (4). When he discussed this abnormality, which he established was an 'inborn error of metabolism,' with Bateson, the latter worked out that it was indeed a hereditary abnormality, and even more importantly that its inheritance followed Mendel's Law of segregation. Much of the genetics terminology that we use today owe their origins to Bateson (5). Over 6000 single-gene disorders are known and many, once fatal, are now manageable with recombinant replacement enzymes.

Although he was no pharmacogeneticist during his lifetime, with his development of the mathematical concepts that allowed Mendel's to develop his theory, Pythagoras has earned his place as one. What is discrete and what is continuous is of course often just an illusion as mathematicians studying wave mechanics have shown us.

Werner Heisenberg (6) showed us that there was much uncertainty in the observation of physical phenomena. We have come to realise that in pharmacogenetics, discrete units of inheritance can produce apparent Darwinian 'blending' when many genes contribute to a trait of interest, such as a drug response. Such traits are described as polygenic. Sometimes matters become more complicated and the traits are also affected by environmental influences as Darwin first surmised. Such traits are referred to as complex polygenic and multifactorial. Skin colour is an example but so are many drug responses. All pharmacists are of course aware of the potential clinical impact of drug-drug and drug-diet interactions.

Much of the early pharmacogenetics work focussed on adverse effects of drugs (7). These included excessive prolongation of the action of suxamethonium (8), and the haemolysis induced by antimalarial drugs, notably primaquine (9,10). The latter case brought us back to Pythagoras as the adverse effect was associated once again with G6PD dehydrogenase (11). Such adverse effects led Motulsky to observe:

*'In discussions of drug idiosyncrasy, careful distinction should be made between toxic reactions caused by immunologic mechanisms (drug allergy) and abnormal reaction caused by exaggeration or diminution of the usual effect of a given dose. Although some progress has been made in the study of mechanisms of drug allergy, little was known until recently about the pathogenesis of hypersusceptibility reactions and hyposusceptibility reactions. Data are available now which suggest that reactions of this type may be caused by otherwise innocuous genetic traits or enzyme deficiencies'* (12).

The genetic basis of several hypersensitivity reactions, previously referred to as idiosyncratic, is now well established (13,14).

## **PHARMACOKINETICS AND PHARMACODYNAMICS**

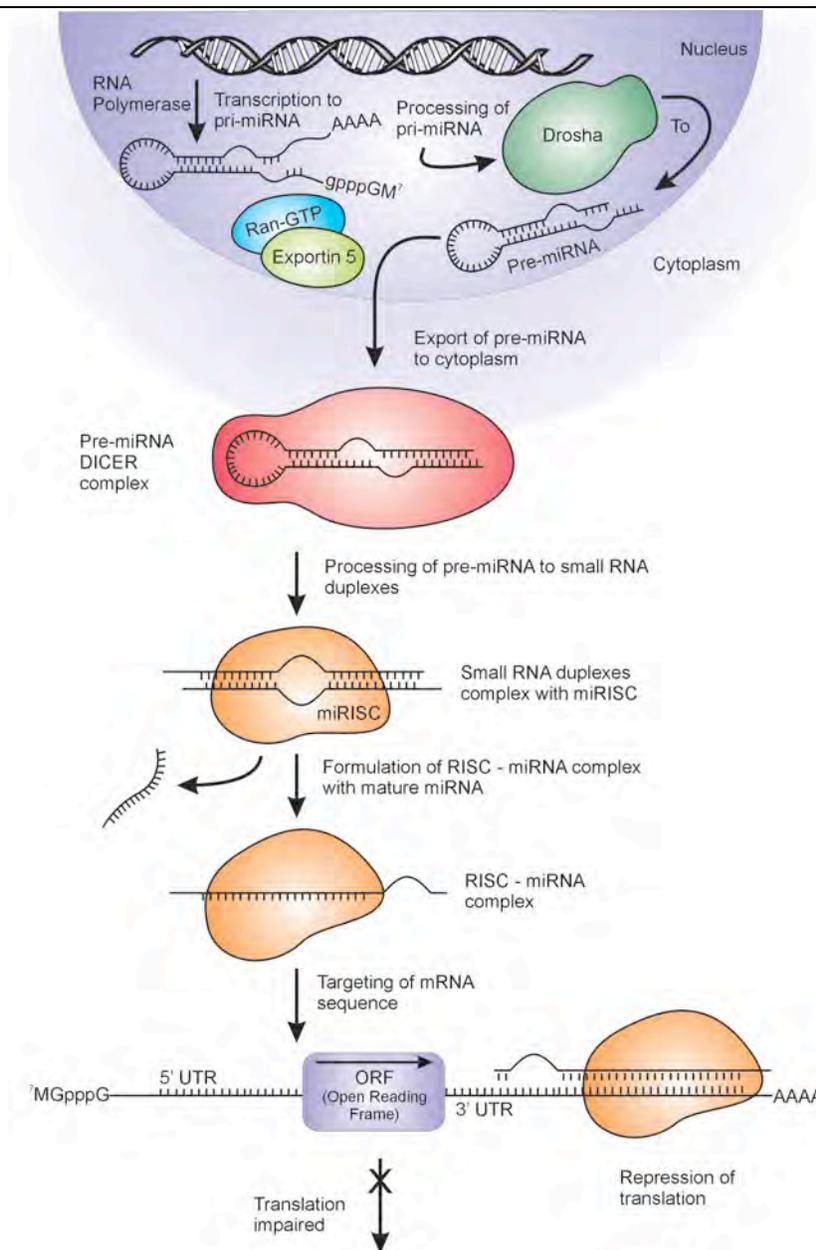
The discovery of the importance of the cytochrome P450 enzymes in the biotransformation of drugs, led to an explosion of studies on the impact of variants of those enzymes on drug action. Those studies coincided with the development of analytical and mathematical methods for probing the disposition of drugs in the body; a field defined by the terms pharmacokinetics and bioavailability. Many members of the cytochrome P450 enzyme superfamily have been identified. Although there was much hope that identification of dysfunctional variants would help us to personalise therapy, in practice the value of such insights has been limited for many reasons, including the following four.

Firstly, our body, like the great city of Madrid or Barcelona, is complex; much more complex. There are many roads leading to and out of it. When one road is blocked, there is usually another road that one can use. So, when one metabolic pathway is blocked, the body uses another pathway to get rid of the drugs it receives.

Predicting the impact of an ineffective enzyme on a drug's action is difficult for a body that has evolved over millions of years. Secondly, the relationships between dose and blood level, and blood level and activity are complex. It is usually better to measure blood level than to predict it from the genetic variants, particularly for drugs with narrow therapeutic windows. That is why for drugs such as vancomycin and tacrolimus, therapeutic blood level monitoring is still the best optimizer. Thirdly, when a pharmacodynamic effect or biomarker of beneficial or adverse effect is measurable it is usually better to use it

than to go one step back to a defective genetic variant. That is why with warfarin, measuring blood clotting (INR; International Normalised Ratio) is better than using genetic algorithms. Well over one hundred studies have shown this. In any case, new drugs that are easier to use than warfarin are available. One day costs will come down to make them more affordable and perhaps make warfarin obsolete.

Fourth, the road from drug to action is long and winding. For example, over one hundred genes are said to be involved in the action and disposition of warfarin.



**Figure 2. Processing and function of microRNAs.**

## EPIGENETICS AND AN EXPANDING RNA WORLD

The study of epigenesis, or the study of the functional impact of DNA modifications that do not involve any

change in DNA sequence, initially applied to the study of embryonic development, now provides considerable insight into the action of drugs, including drug resistance. We know now that the bases that make up DNA are often

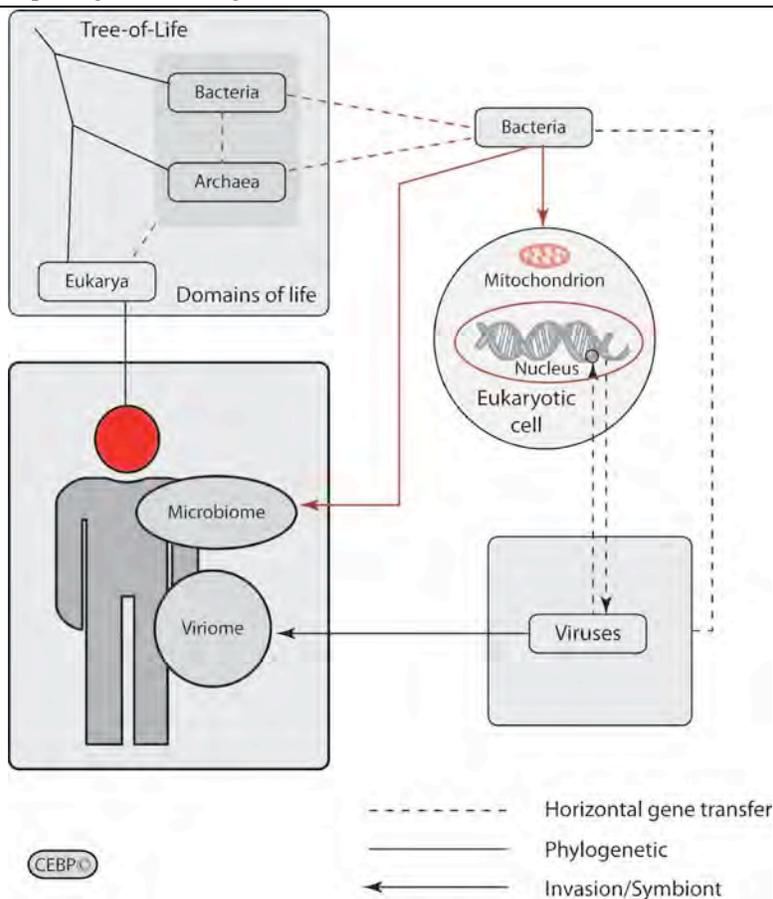
modified to provide control for gene expression.

One of the greatest discoveries of recent years is that RNA molecules are not simply intermediates for translation to protein but that in their many different guises, they have many different functions in gene expression (15). MicroRNAs have attracted significant attention, and understanding their in-vivo processing (Figure 2) is leading to the development of new classes of medicines such as the oligos described below.

**OUR IMMUNE SELF AND IMMUNOTHERAPY**

Quite aside from the ageing process that makes us different with every passing day, we are also continuously shaped by our environment. To survive our body needs specialist cells that act as expert agents to recognise friend

from foe, and for this we have evolved an exquisitely effective immunological surveillance system over evolutionary time: An immediate response innate system that recognises enemies met over evolutionary time, and an adaptive system that remoulds itself quickly to recognise new enemies both from within (e.g. in the form of cancer cells), and from outside, in the form of new microorganisms and new aggressive variants of old organisms (e.g. Zika and Ebola viruses, and new strains of influenza viruses). Cancer can be regarded as a failure of the immune system. Our resident microorganisms (our microbiome; Figure 3) participate more closely in our immunological remoulding than we thought even as recently as two decades ago (16,17).



**Figure 3. Tree of life.**

From the new insights into our immunological system, Behring’s first serum therapy, or antibody therapy, against diphtheria has now expanded into a whole host of immunotherapies, not only against microorganisms but also against cells that have become renegade as cancer cells, and self-molecules that are misrecognised by our immune system as foreign, and molecules that cause atherosclerosis.

**The nature of targeting**

Drug targeting or drug delivery has been on the minds of drug developers ever since Ehrlich proposed his magic bullet theory of drug action (18). His approach was

structural modification of a lead compound to optimise the benefit-harm balance. Salvarsan his first magic bullet was compound 606 in the series he screened. This approach to drug screening is still current and has found new life in the repurposing of existing drugs. The second major approach to optimising drug delivery was through the development of sophisticated dosage forms such as osmotic pumps, transdermal patches. Depot injections, and liposomal systems. Both approaches contributed albeit modestly to the march of medicine towards better therapies.

With the unravelling of the double-helical structure of DNA and detailed understanding of the expression of genes to functional proteins, drug developers began to

dream of targeting DNA itself, first crudely and non-selectively with drugs that intercalated with or broke down DNA, but later more selectively at specific nucleotide sequences with short chains of nucleotides (oligonucleotides or oligos) (19,20). The road for oligos from the laboratory to the bedside has been a long and hard one but recent successes in the form of both licensed medicines (see below) and promising clinical reports suggest that the future may indeed be bright.

### New therapies

From the greater insight into the phenomena which we have mentioned have emerged a whole host of new therapies that even Pasteur and Koch would have wondered at.

- (i) Small molecule targeted agents such as imatinib and gefitinib which have revolutionised the therapy of some cancers (21).
- (ii) Macromolecular agents such as tacrolimus which make possible long-term engraftment of organs sometimes using age-old approaches (22).
- (iii) Exquisitely specific antibodies that tame severe arthritis and skin diseases as well as various cancers.
- (iv) Epigenetic medicines that treat hitherto intractable disease and reverse drug resistance (23).
- (v) Medicines such as ivacaftor that chaperone defective receptor molecules to improve their function (24).
- (vi) Medicines such as bortezomib, a proteasome inhibitor that acts on protein processing and cell-death (25).
- (vii) Antiviral agents that can cure rather than only suppress (26).
- (viii) Gene therapies that have less severe off-target effects and prolong life meaningfully (27,28).
- (ix) Licensed antisense oligonucleotides such as eteplirsen and nusinersen that improve the production of functional proteins in severe muscular dystrophies (29,30).

### FUTURE THERAPIES

Small molecules will no doubt continue to be important but will most likely be increasingly targeted. As such they may require companion diagnostics to optimise their use. Several such drugs are already on the market. Individualisation of therapy will require more pre-prescription testing but great care must be exercised so that unnecessary tests are not introduced (31,32).

We can perhaps also predict that macromolecular and cellular therapies will increase in importance in the form of a widening range of immunotherapies not only for treatment of disease but also for its prophylaxis.

The discovery of how to reprogram somatic cells to pluripotency led to hopes that regenerative medicine could

at last become reality (33). It was hoped that with the use of a patient's own cells (autologous), problems associated with immune rejection and poor engraftment could be overcome. However, clinical success has remained elusive (34) and the use of donor (allogenic) cells for induction might well be the better way forward. The history of the development of therapeutic monoclonal antibodies show us that persistence eventually pays off. Sales of such antibodies not exceed over 50 billion dollars annually (35). A recent report of regeneration of vision with surgical interventions that preserve endogenous stem or progenitor cells provides cause for optimism (36,37).

### ROLE OF THE CLINICAL PHARMACIST

What then is the role of the clinical pharmacist in this new genomic era? Over four decades ago, the American Association of Colleges of Pharmacy, recognising the rapid changes taking place in pharmacy practice commissioned and published an influential report on the future of pharmacy. It recognised that despite *'the real and multifaceted differentiation in the practice roles of pharmacists, there is a common body of knowledge skill, attitudes and behaviour which all pharmacists must possess'* (38). *In redefining pharmacy, they called attention to three key elements: firstly, ready and comprehensive knowledge of drugs, their actions and use; secondly, competencies to serve; and thirdly service to meet both individual and societal needs.'*

I think that, by and large, these elements are still key. For this presentation, I draw attention to another of their main perceptions: *'a lack of an adequate number of clinical scientists who can relate their specialized scientific knowledge to the development of the practice skills required to provide effective, efficient and needed patient services.'* Although as we have indicated, what is a drug has expanded to include an array of immunotherapies and cellular therapies, the main challenge for schools and leaders of pharmacy is probably still the training of sufficient numbers of clinical scientists with expert knowledge of drugs.

It may be fitting to end my presentation with Paul Ehrlich's words, uttered over a century ago:

*'..to allude to my quotation from Bacon, we no longer find ourselves lost on a boundless sea but we have already caught a distinct glimpse of the land which we hope, nay, which we expect, will yield rich treasures for biology and therapeutics'* (39).

Many rich treasures have indeed been discovered. Many more will follow. However, the licensing of targeted agents now involves testing fewer subjects prior to marketing. As custodians of drugs, clinical pharmacists will no doubt wish to ponder on some more of Ehrlich's words:

*'I have before me the records of over 9,000 cases. ... The primary object of these large numbers is to explore the possible dangers of the remedy, because nothing less than an accurate knowledge of these will provide a sound basis for the introduction of a new medicament into general*

*medical use. Indeed, it has often been demanded that in the treatment of man .... only such agents shall be used as are absolutely free from danger. Were one to yield to this demand, any progress of therapeutics, in a chemotherapeutic sense, would be altogether impossible; for substances which are capable of freeing the living body from an infection cannot be regarded as indifferent; there must rather be inherent in them a certain characteristic toxicity' (40).*

The use of medicines always involves important trade-offs and clinical pharmacists may help their patients in better appreciating this.

*Acknowledgments:* The Figures are all taken from the author's *Genomic Medicine 101* (41).

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