The limitations of vacuum tubes (bulkiness, high power consumption, fragility and short life) soon stimulated research into alternative devices to rectify and amplify signals. In 1948, the invention of the transistor was announced by Bell Telephone Laboratories, which resulted in the 1956 Nobel Prize for physics being awarded to John Bardeen, Walter Brattain and William Shockley. The limerick [1] celebrates their invention (the word rube in the penultimate line is slang for an unsophisticated, uncouth person):

Schockley, Brattain and Bardeen,
Commanding electrons unseen,
Made vacuum tubes,
Fit only for rubes,
And those who think progress obscene.

Final analysis

As I have intimated in similar previous articles, the limerick offers an ideal way of presenting science and scientific concepts. In this case, my examples all relate to the theme of the electromagnetic spectrum and in themselves provide a spectrum of detail and information on the discovery and the inventors and scientists involved. It is interesting to note that the scientific limerick has not lost its appeal. Far from it, my collection is growing by the month, although the field of drug discovery and development is still lacking examples!

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In vitro experimental models for the blood–brain barrier

In recent years, *in vitro* experimental models have been widely accepted and applied in drug development. Artificial membranes [e.g. parallel artificial membrane permeability array (PAMPA)] and various cell-based models (e.g. Caco-2) have greatly facilitated the screening of molecules for intestinal permeability. Liver microsomes and hepatocytes are routinely used in the evaluation of metabolic fate (e.g. metabolite identification), metabolic stability and drug–drug interaction potential (e.g. P450 inhibition and induction). Hepatocytes and liver cell lines are commonly used to screen for hepatotoxic potential. These *in vitro* assays greatly facilitate the drug development process because they enable the optimization of drug candidates with appropriate drug-like properties [1].

One area that is lagging behind is the development of a practical blood–brain barrier (BBB) model. The BBB serves as a physiological protective barrier between the central nervous system (CNS) and the systemic circulation. For CNS drugs, ready penetration across the BBB is necessary for efficacy. For non-CNS drugs, non-permeability is preferred to minimize CNS toxicity. Non-permeability is especially important for cytotoxic drugs (e.g. anticancer agents). Therefore, an *in vitro* experimental model that can accurately predict drug BBB permeability in humans will greatly enhance drug discovery and development.

In vivo, the BBB is represented by tight junctions between the endothelial cells of the microcapillary and the glial processes that form 'endfeet' surrounding the microvessels. The barrier thereby consists of the cell membranes of the non-fenestrated endothelial cells and the glial cells, and their respective tight junctions. Furthermore, the endothelial cells possess highly effective drug efflux systems [2], such as the P-glycoprotein (Pgp), which serve to remove xenobiotics that have entered the endothelial cells. A drug that can effectively penetrate the BBB is one that can penetrate through the endothelial cells and glial processes and is not removed from the endothelial cells by the drug efflux mechanisms.

It is now widely accepted that BBB models require the participation of multiple cell types: the brain

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microvascular endothelial cells serve as the major cell type providing the barrier and the non-endothelial cells, such as the perivascular glial cells, promote the formation of the barrier. Primary brain microvesicular endothelial cells (BMEC) co-cultured with astrocytes is the most common approach. Most researchers use bovine [3] or porcine [4] BMEC co-cultured with neonatal forebrain rat astrocytes or a glioma cell line [5].

An acceptable BBB model should have the following characteristics:

- tight cell–cell junctions to reproduce the tight cell barrier *in vivo*;
- active efflux transporters, especially Pgp, to model efflux of substrate molecules;
- active uptake transporters, such as glucose and amino acid transporters, to enable modeling of transporter-mediated drug uptake;
- expression of receptors as observed in BMEC *in vivo* to enable targeting the receptors to enhance drug permeability;
- expression of drug metabolizing enzymes (e.g. γ-glutamyl transpeptidase [6]) to model xenobiotic metabolism;
- similarity in responsiveness to permeation modulators as observed *in vivo* to enable investigation of disease-related or drug treatment-related changes in BBB functions.

Differences among species represent an aspect of the BBB that is often ignored, but one that I believe is important to the usefulness of an *in vitro* BBB model. There are many publications comparing *in vivo* BBB properties in one species (e.g. rat) with an *in vitro* model using cells from a different species (e.g. bovine or porcine), and then drawing conclusions on the utility of the *in vitro* system to predict BBB drug permeability for yet a third species (e.g. man) Although differences among species in drug metabolizing enzymes (e.g. P450 isoforms) have been well studied, the differences in BBB functions are yet to be clearly defined. It is not prudent to assume that such differences are not present or important, especially as there is evidence that illustrates differences among species in Pgp functions [7-9].

Development of a reproducible and practical BBB model that can accurately predict BBB permeability of drugs in humans is a research area that will enhance the efficiency of drug development. Careful definition of the BBB physiology and biochemistry, paying particular attention to crucial differences among species, will guide the development of the most appropriate experimental models.

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Albert P. Li
Advanced Pharmaceutical Sciences
PMB 146
6400 Baltimore National Pike
Baltimore, MD 21228, USA
e-mail: lialbert@apsciences.com

The development of antimicrobials and vaccines against bacterial bioterrorism agents – where are we?

Over the next five years, the US National Institutes of Health (NIH) plan to spend hundreds of millions of dollars to discover and develop or improve treatment and prevention modalities for agents of bioterrorism. The NIH has recently funded eight centers designated as 'Research Centers of Excellence.' These centers have been awarded $350 000 000 to develop new antibiotics and vaccines to protect the US population from agents of bioterrorism, as well as novel means to detect them [1]. Several other programs are currently under consideration and/or development at the NIH to further expand our scientific armamentarium against these agents. Similar funds are being spent to upgrade the sadly neglected public health infrastructure. The salient question is: will this strategy prove successful in protecting the US from future bioterrorism attacks?

In a recent edition of *Drug Discovery Today*, Greenfield and Bronze reviewed many of the key issues surrounding the prevention and treatment of three bacterial agents, *Bacillus anthracis*, *Yersinia pestis* and *Francisella tularensis*, as well as the toxins produced by *Clostridium botulinum*, which are believed to pose the greatest threat as bacterial bioterrorism agents [2]. The research needs for each one of these agents is clearly reviewed and should be an important part of the research agenda of these NIH research centers.

There is a need for clearer understanding of the efficacy of antimicrobial agents against *B. anthracis, Y. pestis* and *F. tularensis*. The strategy of using prophylactic antimicrobials for combating a bioterrorism attack with one of these three agents is well