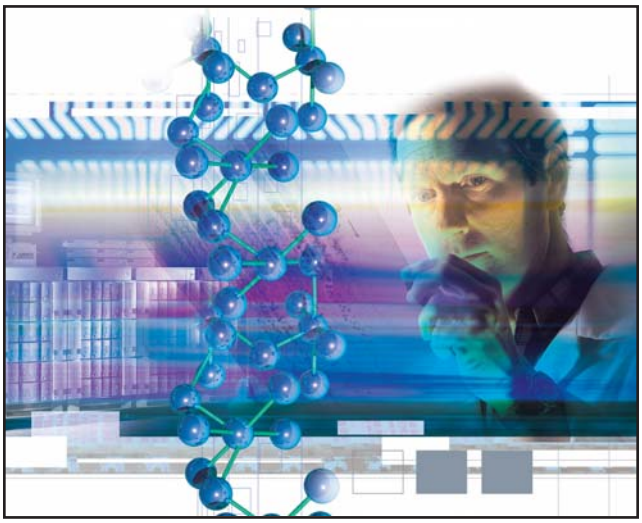
Drug Discovery

Scott E. Walker



Human beings have been in search of compounds to alleviate disease and the symptoms of disease since the beginning of time. Initially, most drugs were obtained from natural sources. Two of the most obvious examples are acetylsalicylic acid (ASA), from white willow, and digoxin, from foxglove.

For some products initially obtained from natural sources, complete or partial synthetic pathways have now been found. ASA represents one of the earliest examples of this evolution. Salicylic acid was first prepared by the Italian chemist R. Piria in 1838 from salicylaldehyde; later, in 1860, it was prepared by the German chemists Hermann Kolbe and E. Lautemann, who used phenol and carbon dioxide. In 1897, Felix Hoffmann, a chemist in the employ of the German dyestuffs company Bayer, managed to acetylate the phenol group of salicylic acid. This compound became the world's first truly synthetic drug, as opposed to materials obtained from natural sources and then purified. Today, ASA is synthesized from dry sodium phenolate and carbon dioxide.[1]

Oral contraceptives represented one of the first instances in which systematic study was used to develop a synthetic compound to mimic the body's natural hormones for use as a drug.[2] Margaret Sanger, the founder of Planned Parenthood, and Mrs. Page McCormick, a philanthropist, encouraged the development of the first oral contraceptives. The first clinical report of the use of oral steroid hormones to suppress ovulation was published by Gregory Pincus and John Rock, from Boston, in 1956. Approval from the US Food and Drug Administration was obtained in 1960, and marketing of the preparations in Britain began 2 years later.[1,2] Since then, numerous novel compounds have been synthesized, tested, and brought to market.

Today, the discovery and synthesis of potent novel drugs is at an all-time high. These compounds have come from plant, animal, insect, and synthetic routes, and we have genetically engineered both plants and bacteria to produce some chemicals. New drugs are rigorously tested for safety and efficacy and are often evaluated for interactions with other compounds. It is therefore somewhat surprising that patients feel the need to turn, in large numbers (10 million Canadians[3]), to alternative therapies. In this issue, Tom Paton and Monique Zamin point out some of the issues that must be considered when alternative medicines are considered for addition to a formulary.[4] Some of these compounds have been demonstrated as beneficial in "clinical studies", although the design of some of this research is of dubious quality.[5] Most patients regard herbal products as safe, largely on the basis that they are "natural", but reports are accumulating to indicate that these compounds can interact with other therapies,[6,7] sometimes with serious consequences.[8] What many patients may also fail to appreciate is that the entire herbal industry is unregulated. This lack of regulation means that these products can be marketed with extravagant claims, but may also be part of the reason that the products have extremely variable and, in some cases, extremely low label claims.[3,9]

continued on page 75

continued from page 72

Because the action of all compounds, regardless of whether they are natural or synthetic, is generally through interaction with a receptor or competition for a body system, the existence of an unregulated segment within the pharmaceutical industry is both scary and unreasonable. The mild regulations accepted by Health Minister Allan Rock[10] on March 26, 1999, should improve this situation but may not go far enough, fast enough.

References

1. Encyclopaedia Britannica. Available at: http://www.britannica.com/ (accessed 2000 Feb 23).
2. BBC News. A short history of the pill. BBC; 1999 Jan 7. Available at: http://news.bbc.co.uk/hi/english/health/newsid_250000/250337.stm (accessed 2000 Feb 23).
3. Papp L. Blind trust: herbal "cures". *The Toronto Star* 2000 Jan 15;Sect A:1,14-15.
4. Paton T, Zamin M. Formulary considerations for botanical products and food supplements. *Can J Hosp Pharm* 2000;53:81-2.
5. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St. John's wort for depression — an overview and meta-analysis of randomised clinical trials. *BMJ* 1996;313:253-8.
6. Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with a herbal extract from St. John's wort (Hypericum perforatum). *Clin Pharmacol Ther* 1999;66:338-45.
7. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. *Lancet* 2000;355:547-8.
8. Ruschitzka F, Meier PJ, Turina M, Lüscher TF, Noll G. Acute heart transplant rejection due to Saint John's wort. *Lancet* 2000;355:548-9.
9. Draves AH, Walker SE. Analysis of the hypericin and pseudohypericin content of commercially available St. John's wort preparations [abstract]. *Can J Hosp Pharm* 2000;53:150.
10. Welcome to the new Office of Natural Health Products (ONHP) opening winter 2000. Ottawa: Health Canada. Available at: http://www.hc-sc.gc.ca/hpb/onhp/welcome_e.html (accessed 2000 Feb 23).

Scott E. Walker, MScPhm, is Editor of *CJHP*.