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The Janus Corner

This occasional section within the journal surveys visions and achievements, often not on the main track of the developing biomedical sciences, but all relating to discoveries and developments of medicinals – both ancient and modern. What they have in common, in one way or another, is providing further background and glances around the edges of the core discipline of pharmacognosy, as it has been and continues to evolve within our times.

Book Review

B Schaefer, Natural Products in the Chemical Industry

(Translated by Smith D and Janssen B), Heidelberg, Springer Verlag 2014, 831 pages. ISBN 978-3-642-54460-6 (also available as an E-book)

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Dear Readers:

Do not be put off or misled by the title of this book. It is in fact a superb overview of the discovery and development of a range of natural products that we now accept as basic medicinals.

It should be required reading for any serious student of Pharmacognosy and its more recent history. Both the author and his most capable translators deserve a special commendation for making so much scientific and medical history so easy to learn.

Throughout all history pharmacognosists have been the custodians of an essential art – knowing how to harness the medicinal benefits of products from micro-organisms, plants and animals. Equally important, this wisdom has to be tempered by its counterpoint i.e. knowing how to limit/avoid intoxications from some of these vast natural resources.

The principal chapters of this quite remarkable book deal with Colourants, Flavours and Fragrances, Aminoacids and then Pharmaceuticals (209 pages), Hormones (77 pages), Vitamins (87 pages) followed by a discussion of some Agrochemicals. Each chapter is preceded by a very brief summary (in bullet points) and many individual items are also cogently summarised, also in the bullet point format. All chapters are copiously illustrated with flow sheets of chemical reactions and by some vivid images of medicinal plants, crop processing, etc. together with a remarkable collection of photo-portraits of pioneering investigators.

The rest of this review focuses mainly upon the fifth and longest chapter dealing with the discoveries of some major pharmaceuticals, all based on understanding the properties of natural products with a profound physiological effect. They include:

(i) Vasodilatory Brazilian snake venoms which contains hypotensive bradykinins (nonapeptides) and led to the ultimate development of ACE and renin inhibitors to control hypertension.

(ii) β-Lactam antibiotics from fungi and bacteria, with tremendous research programmes to avoid necro- and nephro-toxicities and minimise antibiotic resistance. At the time of writing (2013) it was considered that the biotechnological production of penicillins and cephalosporins is clearly superior to chemical synthesis but the carbapenem antibiotics are best obtained by chemical synthesis.

(iii) Opiates: It is salutary to note that analgesics are the most frequently prescribed drugs. Together with antirheumatic agents they accounted for 80% of all prescriptions in 1992.

(iv) Tetrahydrocannabinol and many other phytocannaboids derived from hemp (but also present in some liverworts). This account discusses their biosynthesis and formation of many artefacts generated by heat, light and/or oxygen. Following identification of cannabinoid receptors in the brain and some other tissues e.g. spleen, gastrointestinal tract, Raphael Mechoulam (Hebrew University, Jerusalem) discovered endogenous cannabinoids in 1988; most notably anandamide = arachidonoyl-ethanolamide and arachidonoyl-2-glycerol, the corresponding derivatives of DHA and dihomo-γ-linolenic acid. Anandamide has even been identified in cocoa and chocolate!

(v) Non-steroidal anti-inflammatory drugs (NSAIDs). Hippocrates (460-377 BCE) wrote about the analgesic and antipyretic effects of willowbark, poplar and some evergreen bushes. The history of the development of selective Cox-2 inhibitors is well documented, but no mention is made of the disastrous consequences of Merck's blockbuster inhibitor Rofecoxib (Vioxx) whose adverse (lethal) effects were well known to practising rheumatologists[1-2]

This section also includes a history of pyrazolones, formerly used as cheap and widely available analgesics. They are still frequently used in many European and African countries, e.g. metamizole aka dipyrone.

(vi) Cyclic Prostaglandins (PGs), the target a whole range of non-steroidal

anti-inflammatory drug (NSAIDs) therapy. By contrast, there are fewer drugs available for controlling the alternative oxidation products of arachidonic and related PUFA, the acyclic leukotrienes. The PGs are highly active and exhibit an extraordinary broad spectrum of activities (anti-glaucoma, anti-ulcer, anti-platelet aggregation, etc.) including those promoting the resolution of inflammation, the 'resolvins'.

(vii) Tetrohydrolipostatin (orlistat, Xenical) and other 'lifestyle' drugs that help control appetite or inhibit digestive lipases to treat obesity. Lipostatin (LS) and a number of other microbial lactones selectively and irreversibly inhibit pancreatic lipase. LS contains the four-membered oxetane ring, so it is not readily amenable to mass production via chemical synthesis.

(viii) Taxol® (paclitaxel) was formerly a scarce anti-cancer drug, sourced from the bark of Pacific Yew trees. It inhibits the dis-assembly of intracellular microtubules that precedes cellular proliferation. It is now produced in cultured cells of taxus stimulated by traces of the herbal hormone, methyl jasmonate – effectively raising their taxol content 100-fold.

(ix) Statins (HMG-Co A reductase inhibitors) used to lower blood cholesterol levels. The first natural product compostatin/medastatin a polyketide was isolated from cultures of *Penicillium citrinum*, [It was not active in rats which have low levels of 'unhealthy' LDL, most of their serum cholesterol is bound in healthy HDL.] This was soon followed by medinolin/lovastatin sourced from *Aspergillus terreus*. Thereafter a number of semi-synthetic statins Pravastatin, Rosuvastatin etc. were produced by total synthesis.

(x) Artemisin for malaria. The term 'malaria' is based on the perception that fumes of bad air (It. mala aria) emanated from swamps and cause health problem (p,442), soon to be associated with mosquitoes (GM Lance 1770). Seeds of Cinchona trees from Peru were smuggled to London and on-sold to the Dutch government which established extensive plantations in Indonesia to supply the antimalarial drug quinine. Supplies were effectively cut off in World War II and led to an enormous synthetic program to develop novel antimalarial agents. The Bayer AG Company (Germany) alone tested 12,000 compounds. One of the most effective was chloroquine (Resochin) discovered in 1934 which became a mainstay of antimalarial therapy until mosquitoes acquired drug-resistance.

Interest then shifted towards a traditional Chinese medicine from sweet wormwood (*Artemesia annua*) Quinghao, used for over 1600 years to treat malaria in China. The secret of success proved to be a cold water extraction (not the usual practise of using hot solvents) which preserved the reactive pharmacophore, a peroxide ketal (1,2,4-trioxane) of the active antimalarial, artemisinin. Once again it was found that the phyto-hormone, methyl jasamonate could enhance the formation of artemisin (p.459).

(xi) Caffeine (1,3,7 trimethyl xanthine) is the most consumed psycho stimulant. This alkaloid acts as a mild euphorigen, stimulant or relaxant – rapidly penetrating the blood brain barrier. Theobromine (3,7 dimethylxanthine, originally marketed as a diuretic) is the main alkaloid in the coca bean. Caffeine is a multimodal physical stimulant, raising blood pressure but dilating bronchial vessels. It promotes fat and carbohydrate metabolism by increasing lipases and phosphorylases respectively. Caffeine is removed from coffee by extraction with supercritical solvents e.g. liquefied carbon dioxide, facilitating its inclusion in many non-coffee beverages.

(xii) Nicotine, an alkaloid, is one of the most potent plant toxins. It can induce respiratory paralysis at oral doses <1mg/kg body weight. It is formed mainly in the roots of tobacco plants and transported to the leaves for storage.

Smoking is now considered to shorten the human lifespan by approximately 10 years, due to adverse effects on cardiovascular and digestive systems. Nicotine's toxic effects are harnessed in agriculture e.g. for treating lice and ticks in animals, as a deworming agent (antihelmintic), to eliminate aphids and as a general insecticide in viticulture. This subsection also discusses nicotinoids – various nicotine-related natural products e.g. lobelin, epibatidine, cytisine (from laburnum seeds), anetoxin (from cyanobacteria) all causing hepatoxicity and neurotoxicity. Cytisine became the lead structure for the development of Varenicline (Pfizer) an aid for smoking cessation which attenuates the effects of nicotine.

This chapter has 569 references and a truly remarkable collection of images of plants, people and historical documents.

Chapter 6 entitled "Hormones" with 131 references provides an equally fascinating account focussing particularly on the development of:

(i) steroids and hormonal contraceptives,

(ii) thyroxine and

(iii) adrenaline and other sympathomimetic amines and the agents that bind selectively to at least six types of adrenergic receptors.

Chapter 7 entitled "Vitamins" documents the roles of 13 of these essential biochemical co-factors, not synthesised in sufficient quantities, if at all, in the human body. It particularly deals with:

(i) Vitamin A and carotenoids, now produced in genetically modified marigolds to increase the yield of astaxanthin. (This pigment is also unmasked in cooked lobsters.) Plants and algae are still important sources of carotenoids. To combat Vitamin A deficiency which can cause irreversible blindness, xerophthalmia, etc., 'golden rice' strains have been engineered to contain β-carotene in their endosperm.

(ii) Vitamin D deficiency is linked to low exposure to sunlight or lack of access to vitamin supplements, e.g. cod liver oil, is a very important pre-hormone for renal and hepatic synthesis of calcitriol via two hydroxylation reactions. New approaches to production are based on using selective microbial hydroxylases. Calcitriol is now recognised as an immunostimulant, a rather new concept that expands the functions of Vitamin D beyond being a prime facilitator of calcium metabolism.

(iii) Biotin (Vitamin H). This has been an enormous challenge to synthetic chemists having three stereogenic centres in a 9-carbon molecule. Only one enantiomer shows full biological activity. Because of its extensive biogenesis by gut flora, nutritional biotin deficiency is rare but it may become a problem after prolonged antibiotic therapy.

On reflection

It helps to have some appreciation of the evolution of the contemporary, almost universal practises of using tonics, prescription drugs, herbal medicines and nutritional supplements to combat sickness and sustain wellbeing.

So this book is a truly amazing resource for finding out about the history and origins of major classes of drugs we use today; their benefits and shortcomings, the commercial practicalities of production etc. It is salutary (literally good for health) to understand how dependant we still are on the natural resources providing essential raw materials e.g. opium poppies for extracting morphine - but also for providing enzymes to bring about key chemical transformations.

This is well illustrated by the drug cortisone. The traditional source, adrenal cortex of some (not all) animals was insufficient and too costly to meet the enormous demand for cortisone in anti-inflammatory and anti-shock therapies. Chemical synthesis from deoxycholic acid (DCA) obtained from ox bile relied upon a complex series of over 40 chemical

transformations. A particular problem was to delete the 12-hydroxy group of DCA and introduce an 11-oxy group instead. This problem, a real bottleneck for efficient synthesis, was brilliantly overcome by Peterson and his colleague working in the research laboratories of the Upjohn Company (Kalamazoo, Michigan). They harnessed a microbial 11α-hydroxylase to produce epicortisol, which could then be oxidised to the corresponding ketone, cortisone. This was then selectively reduced to the 11β-alcohol (cortisol), the required hormonal drug.

There were many implications of this achievement nearly 70 years ago including: a) the successful adoption of various cells (microbial, insect, etc.) that could be 'engineered' and cultivated *in vitro* as a source of biochemical catalysts and b) scaled up to grow in biofermenters that could operate 24 hrs/day and c) immensely reduce the production of chemical waste products – in some cases by as much as 95%. Another reason to rely on a natural synthetic route was the opportunity to obtain drugs with reactive 4-membered rings e.g. as in penicillin or orlistat. It was interesting to see how the classical synthetic chemists could not produce penicillin for over 30 years and to reflect that its correct structure was deduced from observations by two physical chemists at Oxford UK, Harold Thompson using infrared spectroscopy and Dorothy Hodgkin by applying the technique of X ray diffraction. Both these techniques finally established that the production of a 4-membered heterocyclic ring was possible in nature, if not in the laboratory (at that time). It also removed the rather crippling dogma that 4-membered rings were too unstable to exist – which was wrong. It did however explain their antibiotic activity, being very labile acylating agents (which was right).

Finally we should also note the 'bad news' associated with the development of some of these drugs. Repeatedly, important discoveries were ignored, forgotten or somehow lost. If they had been acted upon decades earlier they might have saved many lives or at least averted much suffering. Three examples will illustrate this regrettable neglect:

a) Vitamin C as found in fresh vegetables and citrus fruits was noted to prevent scurvy by an Austrian physician JG Kamer (1684-1744) and a British naval surgeon J Lind (1760-1794). Yet it was almost 80 years before Lind's discovery led to the compulsory inclusion of lime juice on all British ships sailing south of the Equator;

b) Edward Duchesne (1874-1912), a French army physician serving in Lyon, noted that a fungal infestation could eliminate bacterial growth. He reported this in 1897 as a written communication sent to the Pasteur Institute in Paris, where it was ignored for nearly 20 years. This would have preceded Alexander Fleming's discovery of penicillin by almost 30 years

c) It was 25 years after the synthesis of the steroid drospirenone before it was introduced as a third generation oral contraceptive in combination with estrogen (Yasmin®, Angeliq®).

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A postscript from the editor: Perhaps readers would like to add other instances of regrettable oversights (or outright prejudice) that significantly affected the history of pharmacognosy and associated/ cognate health sciences.

The Consumption of Dark Chocolate Reduces Stress and Inflammation and Improves Memory and Immunity

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Two studies presented at the recent Experimental Biology 2018 annual meeting in San Diego,[1-2] USA demonstrate that the consumption of dark chocolate with a minimum cacao concentration of 70% have positive impacts on cognition, memory, mood, immunity and inflammation. The first of these studies assessed the electroencephalography (EEG) response following the consumption of 48g of dark chocolate containing 70% cacao and reported behavioural and brain health benefits.[1] The other study examined the effects of consumption of the same high cacao chocolate on gene expression in human immune and dendritic cells.[2] Cacao consumption was reported to upregulate T-cell activation signalling pathways and cellular immune responses, as well as some genes linked with neural signalling and sensory perception. The investigators have highlighted cacao flavonoids as being important for these effects as several of these compounds are known to be potent antioxidants and anti-inflammatory agents. Furthermore, they have also been implicated in known mechanisms that are beneficial to brain and cardiovascular health.

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A Compound Isolated from *Justicia gendarussa* Brum. f. is a Better Inhibitor of HIV than AZT

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Justicia gendarussa Brum.f. (Commonly as willow-leaved justicia) is a Asian plant which grows in India, China, Sri Lanka and Malaysia. It is used in several traditional medicine systems for a variety of purposes including rheumatism and asthma. However, a recent study has reported that it contains the arylnaphthalene lignin glycoside patentiflorin A.[3] This compound was reported to have significantly better inhibitory effects against several HIV-1 isolates than the anti-HIV drug AZT. Like AZT, patentiflorin A blocks the decoding of the viral RNA into a DNA molecule by blocking the enzyme reverse transcriptase. However, patentiflorin A was substantially stronger than AZT and it also inhibited AZT-resistant HIV-1 strains, making it a promising new drug lead.

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