The Making of a Modern Medicine by **Dr Ralph White**

Dr White began by saying a drug arrives when it gives rise to a publication! Getting a drug to market is an expensive process and can take 10 to 15 years – few recoup their development costs, let alone the costs of the 13 out of 14 drug hopefuls that fall by the wayside.

Drugs operate by biological mechanisms: natural remedies contain drugs, which can be more effective if purified, or chemically modified. Knowledge of the human genome enables the pathways of bodily functions to be understood, and how they can be upset by diseases. Scientifically the process is one of unpicking molecular complexities. There are thousands of plausible targets.

Antidepressants are big business. They work for about 10% of people, do virtually nothing for 80% and make about 10% worse. Breast cancer is another disease which, when the woman has the right genetic make-up, can be treated with Herceptin – but it does not suit all women. 'One size does not fit all' applies to treatment with drugs. However with individual genetic analysis becoming practicable, a movement towards targeted drug prescription is beginning.

Drugs need to penetrate the cell wall (which is made of cholesterol) of the target cells, through the normal channels which penetrate it. Nerve cells conduct by ion exchange through the cell wall - one is aware of nerve conduction if when stubbing a toe – one will shout out, look round, and massage the toe. Nerves can be stopped for 2 hours or so with a local anaesthetic (often cocaine or a derivative), after which the liver will have cleared it. This is reversible – except with a sushi puffer fish.

The study of **rare diseases** can elucidate bodily processes; about 270 organisations are looking at them.

Cancer. In normal tissue cells divide to replace dying cells, but stop when sufficient new cells are produced. This is enabled by Epidermal Growth Factor Receptors (EGFR) in the cell wall – cell division is initiated when two of these are primed externally and form a pair. However a cell mutation, not caught by normal repair mechanisms, can result in too many EFGRs - and continuous division of cells to form a tumor; the tumor will then get its own bespoke blood supply. There is a drug that inhibits EFGRs, and it is effective in many cases; but, like HIV, other factors are involved… Some cancers can be treated as a controllable chronic condition. Others proliferate so slowly that they are no bother and are only found post mortem. There is a question as to whether breast cancer is over treated.

Drug Development. Very A molecule may be developed as a drug for a target disease. If successful in trials its manufacture will need to be scaled up. This must begin with available materials; alternative methods of synthesis may make for fewer or simpler steps in the process, or give better yields. A variant of the molecule may do the same job but be more economical to make. Antibodies can be developed to bring the patient's immune system into play against a new or otherwise untreatable condition; if developed in, for instance, mice some re-engineering will be needed to present a human signature to avoid rejection.

Early clinical studies are done with healthy people, anonymously. A development plan will set out a Study Protocol and seek Ethical Approval. A Clinical Research Organisation, usually based in a big hospital, will oversee Investigation Centres; these will recruit volunteers, having informed them of the benefits and risks.

Drug Delivery. This should maximise exposure of the drug where it is wanted (and minimise the dose), and minimise any side effects. Very few drugs can be given orally – tablets can get them through the stomach, but then they (or a proportion of them) must survive being eaten up by the liver – dosage can be a problem. One drug, Tamiflu, has a two part structure – the liver parts off the carrier part and releases the active part.

Injection of biologics gets the drug directly into the blood stream; as do inhalers by absorbtion through the lungs. Once in the blood the drug will circulate until it is trapped by its target receptor channel in the cell wall of the target cell. The Blood-Brain barrier stops most things, but lets antidepressants (including alcohol) through.

Pharmacodynamics; and **Pharmacokinetics** – studies of: what the drug does to the body; and what the body does to the drug.
These look at such questions as: Where did it go? How much got in? What metabolites were produced? Interactions with other drugs (or chemicals in food) are being mapped – these are sometimes enhancing – sometimes deleterious - or both. (People prescribed statins should NOT have grapefruit juice. Alcohol and aspirin should not to be taken together.) Cross correlation with tissue histopathology results can help.

What of the future?
- A global product strategy will arise, with universal (instead of country by country approvals);
- New molecules will be developed, and existing molecules will be used in new medications;
- Diseases will be treatable at an earlier stage, and more diseases will be treatable;
Dr White closing remark was that a low cost would be appreciated !