

Unit 5: Free Radicals Pharmacology and Recent Advances in Treatment

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5.1 Free radicals and reactive species: generation

A **free radical** is an atom or molecule carrying an unpaired electron, which makes it hungry to steal an electron from whatever it meets. The family that matters in medicine is the **reactive oxygen species (ROS)**: the superoxide anion radical, hydrogen peroxide (not a radical but the diffusible parent of worse things), the hydroxyl radical (the most destructive, made when peroxide meets ferrous iron in the Fenton reaction), singlet oxygen, and the reactive nitrogen species nitric oxide and its toxic marriage with superoxide, **peroxynitrite**. Sources are built into normal life: the mitochondrial electron transport chain leaks electrons onto oxygen (the largest endogenous source, growing with age and hyperglycaemia), the **NADPH oxidases** of phagocytes make superoxide deliberately as a weapon (the respiratory burst that kills bacteria, absent in chronic granulomatous disease), xanthine oxidase in reperfused tissue, uncoupled nitric oxide synthase, peroxisomes, and cytochrome P450 reactions; outside sources add cigarette smoke, ionising radiation, ultraviolet light, air pollution and redox cycling drugs such as doxorubicin. In small controlled amounts ROS are signals (they tune vascular tone, insulin signalling and immune defence). Disease is **oxidative stress**: production outrunning defence, so radicals attack membrane lipids (chain reactions of lipid peroxidation), proteins (carbonylation, enzyme inactivation) and DNA (strand breaks and mutagenic bases such as 8 hydroxydeoxyguanosine).

5.2 The antioxidant defence and its pharmacology

Defence is layered, and each layer is a drug target or a drug. **Superoxide dismutase** converts superoxide to hydrogen peroxide; **catalase** and **glutathione peroxidase** (a selenium enzyme fed by reduced glutathione, GSH) convert peroxide to water. **Glutathione** itself, the cell's main soluble reductant, is regenerated by glutathione reductase using NADPH. Non enzymatic scavengers patrol the phases: **vitamin E** (alpha tocopherol) breaks lipid peroxidation chains inside membranes, **vitamin C** scavenges in water and regenerates vitamin E, and urate, albumin and bilirubin add smaller contributions. Metal binding is defence too: transferrin, ferritin and caeruloplasmin keep iron and copper away from the Fenton reaction. The pharmacological entries: **N acetylcysteine** supplies cysteine, the limiting building block of glutathione, and is the antidote that saves the liver in paracetamol poisoning, where the radical like metabolite NAPQI has exhausted GSH; it is also a mucolytic by breaking disulfide bonds. Melatonin, the pineal night hormone of section 4.8, is itself a scavenger with antioxidant claims. Edaravone, a radical scavenger licensed in some countries for stroke and motor neurone disease, shows the idea translated into a drug. The honest caveat closes the section: the chemistry is certain, the defence system is real, but flooding the system with vitamin antioxidants in trials has repeatedly failed to prevent cardiovascular disease or cancer and sometimes harmed, because ROS signalling is physiological and oral scavengers rarely reach the radical's birthplace at the right concentration. Antioxidant pharmacology works when it is targeted (NAC against a defined glutathione deficit), not when it is a slogan.

5.3 Free radicals in diabetes

Hyperglycaemia floods mitochondria with glucose derived fuel, and the overfed electron transport chain leaks superoxide. That single upstream event activates the four damaging pathways of diabetic complications in the unifying hypothesis: the polyol pathway, advanced glycation end product (AGE)

formation, protein kinase C activation, and the hexosamine pathway, each adding its own radicals and inflammatory signalling. The anatomical results are the microvascular complications: retinopathy, nephropathy and neuropathy, and accelerated atherosclerosis. Endothelial nitric oxide is quenched by superoxide into peroxynitrite, so diabetic vessels lose their main dilator and protector, a molecular account of diabetic endothelial dysfunction. The therapeutic reading is not a vitamin: it is glucose control itself (cutting radical production at source), renin angiotensin blockade, statins with their pleiotropic antioxidant effects, and the modern agents of section 5.10 whose organ protection exceeds their glucose lowering.

5.4 Free radicals in neurodegenerative disease

Neurons are radical vulnerable: high oxygen use, membranes rich in peroxidisable polyunsaturated fat, modest antioxidant reserves, and, in the substantia nigra, iron and dopamine chemistry that generate radicals as by products. In **Parkinson's disease**, dopamine metabolism by monoamine oxidase produces hydrogen peroxide, neuromelanin binds iron, glutathione is lost early, and the complex I defect of mitochondria mirrors the action of the toxin MPP⁺, which is why oxidative stress sits inside every account of nigral death. In **Alzheimer's disease**, amyloid beta promotes radical generation and is itself modified by oxidation, metal ions (copper, zinc, iron) concentrate in plaques, and oxidative damage markers precede symptoms. The pharmacological attempts match the theory and share its disappointments: selegiline (section 5.8) was hoped to be protective as an MAO B inhibitor, vitamin E delayed some milestones in one large trial without preventing disease, and edaravone's licence is for motor neurone disease, where excitotoxic and oxidative injury converge. Free radicals in neurodegeneration are best taught as established participants whose blockade has not yet become therapy, which is exactly why they belong in a recent advances unit.

5.5 Free radicals in cancer: a double edged sword

Radicals both cause and cure cancer, and the unit insists on both edges. As causes: chronic oxidative DNA damage mutates tumour suppressor genes and oncogenes, and chronic inflammation (hepatitis, colitis, reflux) is a radical factory, which is one account of why chronic inflammation precedes malignancy; AGEs, smoke and radiation enter by the same door. As cures: radiotherapy kills largely by radical mediated DNA damage, and several cytotoxics (anthracyclines, bleomycin, platinum agents) lean on oxidative injury, so tumours with strong antioxidant up regulation (through the NRF2 pathway) are therapy resistant, and there is real concern that high dose antioxidant supplements during treatment protect the tumour as well as the patient. Prevention claims need the same scepticism as section 5.2: beta carotene supplements increased lung cancer in smokers in two large trials, the antioxidant era's most important negative result. The mature position: oxidative stress is a genuine carcinogenic mechanism and a genuine therapeutic weapon, and indiscriminate scavenging in a patient with cancer is pharmacology applied backwards.

5.6 Recent advances in the treatment of Alzheimer's disease

Alzheimer's pharmacotherapy was for decades symptomatic only: **cholinesterase inhibitors** (donepezil, rivastigmine, galantamine) raising the failing cholinergic signal, and **memantine**, an NMDA receptor antagonist damping glutamate excitotoxicity, each buying modest time without altering the disease course. The advance of this decade is the **anti amyloid monoclonal antibodies: lecanemab** and **donanemab** bind aggregated amyloid beta and clear plaques measurably on PET imaging, and in early Alzheimer's disease they slow clinical decline by roughly a quarter to a third over eighteen months, the first disease modifying effect ever shown. The costs are equally specific: **ARIA**, amyloid related imaging abnormalities of brain swelling and microhaemorrhage, riskier in APOE epsilon 4 carriers and patients on anticoagulants, demanding MRI monitoring; intravenous infusions; and a benefit measured in months of slowed decline, not recovery. Aducanumab, the controversial first approval, was withdrawn from the market, a lesson the class

carries with it. Tau directed and anti inflammatory agents remain investigational. The correct examination summary: amyloid is now a proven, druggable, modestly rewarding target in early disease, and diagnosis has shifted to biomarkers because treatment must start before dementia is advanced.

5.7 Recent advances in the treatment of Parkinson's disease

No drug yet slows the loss of nigral dopamine neurons, so advances in Parkinson's disease are advances in delivering dopamine replacement more smoothly and in reaching the non motor disease. **Levodopa** with a dopa decarboxylase inhibitor remains the most effective treatment, and the modern work attacks its fluctuations: **COMT inhibitors** (opicapone) and **MAO B inhibitors** (safinamide, rasagiline) extend each dose; **istradefylline**, an adenosine A2A antagonist, cuts off time by a non dopaminergic route; inhaled levodopa and subcutaneous or intestinal gel infusions (levodopa carbidopa intestinal gel, foslevodopa infusions) rescue patients from oral unpredictability; and **amantadine** in extended release treats the dyskinesias the treatment itself creates. Deep brain stimulation remains the device counterpart for selected patients. On the horizon, alpha synuclein immunotherapies have so far disappointed in trials, and GLP-1 receptor agonists are under investigation for neuroprotection: the honest verdict is a field superb at symptomatic engineering, still waiting for its first disease modifier.

5.8 Recent advances in the treatment of cancer

Beyond the targeted and immune therapies of Unit 3, three advances define the current era. **Immune checkpoint inhibition has widened and moved earlier**: combinations and use in adjuvant and neoadjuvant settings, guided by biomarkers (PD-L1 expression, microsatellite instability, tumour mutational burden), and the management of immune toxicity is now a specialty of its own. **Antibody drug conjugates** deliver chemotherapy on antibody guidance: trastuzumab deruxtecan carries a topoisomerase I poison to HER2 expressing cells (including the newly recognised HER2 low breast cancers) at intracellular doses free chemotherapy could never reach. **Cellular therapy** manufactures the drug from the patient: CAR T cell therapy re engineers the patient's T cells with a chimeric antigen receptor against CD19 or BCMA and has produced durable remissions in B cell leukaemias, lymphomas and myeloma, at the price of cytokine release syndrome and neurotoxicity that units must be trained to treat. KRAS G12C inhibitors (sotorasib, adagrasib) drugged a target called undruggable for forty years, and PARP inhibitors exploit synthetic lethality in BRCA mutated tumours: the pattern of the era is mechanism first, cancer type second, with basket trials organised by mutation rather than organ.

5.9 Recent advances in the treatment of diabetes mellitus

Diabetes care has been re founded on organ protection. The **GLP-1 receptor agonists** (semaglutide, dulaglutide, and the dual GIP GLP-1 agonist **tirzepatide**) amplify glucose dependent insulin secretion, suppress glucagon and appetite, and produce weight loss and cardiovascular outcome benefits that older agents never showed; oral semaglutide exists, weekly injections are standard, and these drugs now treat obesity in their own right. The **SGLT2 inhibitors** of section 1.6 have grown from glucose drugs into heart failure and chronic kidney disease therapy used even without diabetes. Technology is the third advance: continuous glucose monitors replacing finger prick testing, insulin pumps, and hybrid closed loop systems in which an algorithm doses insulin from sensor readings minute by minute, an applied chronopharmacology of section 4.8. Once weekly basal insulin and glucose responsive smart insulins are in late development. Against all of this, the syllabus's oral hypoglycemics of Unit 1 remain the economic backbone for most of the world's patients, and the examination expects both stories at once.

Frequently Asked Questions

Q: Why do thionamide antithyroid drugs take weeks to control hyperthyroidism if they block hormone synthesis at once? Because they block only new synthesis. The thyroid stores weeks of preformed T4 and T3 in the colloid, and that store is released and used while synthesis is already stopped. Circulating T4 also has a half life of about a week. Clinical control therefore lags biochemical blockade by three to eight weeks, which is why beta blockers carry the patient through the early weeks.

Q: How can metformin lower blood glucose yet almost never cause hypoglycaemia when used alone? Metformin reduces hepatic glucose output and improves insulin sensitivity, but it does not stimulate insulin secretion. When glucose falls toward normal, the body's own counter regulation is intact and there is no forced insulin pushing it lower. Hypoglycaemia is the signature of the secretagogues (sulfonylureas and meglitinides), which close beta cell potassium channels regardless of the glucose level.

Q: Why must corticosteroids never be stopped suddenly after prolonged therapy? Exogenous corticosteroids feed back on the hypothalamus and pituitary exactly like cortisol, suppressing CRH and ACTH, and the unstimulated adrenal cortex atrophies. Stop the tablets abruptly and the patient has no cortisol response to stress: the result can be an adrenal crisis of hypotension, vomiting and collapse. Prolonged courses are tapered, and patients carry steroid cards so that illness or surgery triggers extra cover.

Q: Beta lactamases and MRSA both defeat penicillins. How do the mechanisms differ? Beta lactamases are route 1 resistance: bacterial enzymes that hydrolyse the beta lactam ring before the drug reaches its target, answered by penicillinase proof structures and beta lactamase inhibitor combinations such as co amoxiclav. MRSA is route 2: the *mecA* gene gives the bacterium a replacement target, the penicillin binding protein PBP2a, which beta lactams bind too weakly to inhibit, so the wall is built regardless of the drug. No inhibitor fixes a changed target; treatment needs an agent that binds PBP2a (ceftaroline) or a different class altogether (vancomycin).

Q: Why is drug sensitive tuberculosis treated with four drugs when one drug can kill the bacillus in a dish? Because a cavitary lesion holds billions of bacilli, among which mutants resistant to any single drug already exist by chance. One drug kills the susceptible majority and selects the resistant minority, which then multiplies into incurable disease. Four drugs with unrelated resistance mechanisms mean a bacillus must carry several rare mutations at once to survive, which essentially never happens. The drugs also divide the work: isoniazid kills dividing bacilli, rifampicin and pyrazinamide kill the persisters that would otherwise relapse.

Q: Why does vivax malaria relapse after chloroquine treatment, and what does primaquine add? Chloroquine and the blood schizonticides clear the red cell stages, but *Plasmodium vivax* and *P. ovale* leave dormant liver forms, hypnozoites, untouched, and these wake weeks or months later to restart the blood infection. Primaquine is the drug that kills hypnozoites, the radical cure, given after the blood stages are cleared. Its limit is oxidative haemolysis in glucose 6 phosphate dehydrogenase deficiency, so that risk guides testing and dosing.

Q: How do ciclosporin and tacrolimus suppress immunity at the molecular level, and why are blood levels monitored? Both enter T cells and bind an immunophilin (ciclosporin to cyclophilin, tacrolimus to FKBP), and the complex inhibits the phosphatase calcineurin. Without calcineurin the transcription factor NFAT stays phosphorylated and outside the nucleus, interleukin 2 is never transcribed, and T cell clonal expansion stalls at its first step. Levels are monitored because both drugs have narrow therapeutic indices, CYP3A4 driven interactions, and nephrotoxicity that rises with exposure while rejection rises when levels fall.

Q: Proton pump inhibitors are irreversible blockers, yet they are dosed once a day, before breakfast. Why? The covalent bond is to the pump molecule, not the patient: acid secretion returns as new pumps are made, over about a day and a half. PPIs themselves vanish from plasma within hours and can only bind pumps that are inserted in the membrane and actively secreting, and the largest wave of pumps is activated by the first meal of the day. Dosing shortly before breakfast therefore puts peak drug concentration in front of the maximum number of working pumps.

Q: What does chronopharmacology add to prescribing, beyond dose and route? Timing. The body that receives the drug changes across 24 hours: airways narrow near 4 am, blood pressure surges on waking, cholesterol synthesis peaks at night, and acid secretion peaks at night. Chronotherapy matches the dose to the rhythm: evening dosing of short acting statins such as simvastatin, overnight weighting of asthma controller cover, bedtime dosing of H2 blockers in the classical ulcer regimens, and basal insulin arranged against the dawn rise in glucose. Same drug, same dose, different hour, different result.

Q: Lecanemab is called disease modifying in Alzheimer's disease. What does it actually do, and what limits it? Lecanemab is a monoclonal antibody that binds aggregated amyloid beta and clears plaques from the brain, the first intervention to slow the underlying decline rather than only ease symptoms: in early Alzheimer's disease it slowed clinical decline by roughly a quarter to a third over eighteen months. The limits are that it slows rather than stops or reverses disease, it works only in early stages confirmed by biomarkers, and it carries ARIA, brain swelling and microhaemorrhage, especially in APOE epsilon 4 carriers, so MRI monitoring is part of the treatment.

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