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Medicinal Chemistry-Fusion of Traditional and Western Medicine

Third Edition

Robert E. Smith

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MEDICINAL CHEMISTRY - FUSION OF TRADITIONAL AND WESTERN MEDICINE

Third Edition

Authored By

Robert E. Smith

Adjunct Assistant Professor, Park University and Consultant
Science Advisor, United
States Food and Drug Administration (FDA)
U.S.A

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Author: Robert E. Smith

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CONTENTS

FOREWORD i

PREFACE ii
CONFLICT OF INTEREST ii
ACKNOWLEDGEMENTS ii

DEDICATION iv

CHAPTER 1 PERSONALIZED MEDICINAL CHEMISTRY 3
INTRODUCTION 3
METHODS 19
PCR 19
TOF-MS 21
Next-Generation Sequencing (NGS) 22
Pharmacogenomics 27
Effects of Drugs on Metabolism 28
APPLICATIONS 36
KEY POINTS 57
ABBREVIATIONS 57
REFERENCES 61

CHAPTER 2 BIOLOGY OF INFLAMMATION 69
KEY POINTS 83
ABBREVIATIONS 84
REFERENCES 85

CHAPTER 3 METABOLIC SYNDROME, DIABETES, HEART DISEASE AND STROKE 88
GLUCOSE AND ENERGY PRODUCTION 89
METABOLIC SYNDROME 92
DIABETES AND SMOLDERING INFLAMMATION 98
TREATMENTS AND POSSIBLE CURES FOR DIABETES 110
PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS, PPARS 111
RXR PROTEINS 113
LXR PROTEINS 114
FXR PROTEIN 115
CONSTITUTIVE ANDOSTANE RECEPTOR (CAR) 115
RETINOIC ACID-RELATED ORPHAN RECEPTOR (ROR) 116
TAK1 RECEPTOR 116
TREATMENTS FOR OBESITY 117
STROKE 119
MYOCARDIAL INFARCTION OR HEART ATTACK 120
PREVENTING AND TREATMENTING HEART DISEASE 125
KEY POINTS 131
ABBREVIATIONS 132
REFERENCES 134

CHAPTER 4 BIOLOGY OF CANCER: GENETICS, BIOMARKERS AND CLINICAL APPROACHES ... 138

INTRODUCTION 138
ANGIOGENESIS 144
ROLE OF THE IMMUNE SYSTEM 147
DIAGNOSIS AND PROGNOSIS 149
CLASSIFICATION FOR CANCER DEVELOPMENT 150
CAUSES OF CANCER 151
THE CELL CYCLE AND RTKS 152
ROLE OF VIRUSES IN CAUSING CANCER 154
THE ROLE OF THE P53 ONCOPROTEIN 155
ONCOGENES AND ONCOPROTEINS 157
ADVANCES IN TREATING BREAST CANCER 160
AROMATASE 163
VEGF 163
PI3K/AKT/MTOR PATHWAY 165
IGF-1 167
INFLAMMATORY BREAST CANCER 168
EARLY DETECTION 169
LUNG CANCER 172
SKIN CANCER 173
MICRORNAS 174
CANCER STEM CELLS 174
TELOMERASE 176
MUTATIONS IN SOMATIC AND GERMLINE CELLS 176
ROLE OF CYP450 ENZYMES 179
CANCER GENOMICS 179
CANCER EPIGENETICS 180
MUTATIONS 182
MEDICINAL CHEMISTRY POINT OF VIEW 183
KEY POINTS 188
ABBREVIATIONS: 189
REFERENCES 191

CHAPTER 5 MEDICINAL CHEMISTRY AND THE ENDOCRINE SYSTEM 198
HYPOTHALAMUS 199
PINEAL BODY (EPIPHYSIS) 203
PITUITARY GLAND (HYPOPHYSIS) 204
THYROID 206
ALIMENTARY SYTEM 208
KIDNEYS 210
ADRENAL GLANDS 213
REPRODUCTIVE SYSTEM 214
THE HEART AND SKELETAL MUSCLES 217
BONES AND SKELETAL SYSTEM 219
CALCIUM REGULATION 222
TARGETS 223
DIFFUSE NEURO-ENDOCRINE SYSTEM 224
MAJOR ENDOCRINE SYSTEMS 224
DISEASES 225
KEY POINTS 226
ABBREVIATIONS 228
REFERENCES 230

CHAPTER 6 REPRODUCTIVE MEDICINE, OSTEOPOROSIS 234
KEY POINTS 251
ABBREVIATIONS 252
REFERENCES 253

CHAPTER 7 THE NERVOUS SYSTEM 256
INTRODUCTION 256
Components of the Nervous System 259
Neurotransmitters 269
Neuropeptides 274
Nitric Oxide and Carbon Monoxide 277
Glial Cells 279
Pain Control 282
Drugs to Help People Stop Smoking [1] 287
Drugs That Treat Neurodegenerative Diseases 287
Inflammatory Cytokines 289
Parkinson's Disease 290
Alzheimer's Disease 290
Epilepsy 296
Anxiety Disorders 297
Depression 297
Antipsychotics 299
Autism 299
Amyotrophic Lateral Sclerosis (ALS) [1] 300
Damaged Spinal Cords 301
Medicinal Chemistry Point of View 301
KEY POINTS 310
ABBREVIATIONS 313
REFERENCES 315

CHAPTER 8 THE IMMUNE SYSTEM AND IMMUNE NETWORK 323
IMMUNE NETWORK 327
COMPONENTS OF THE IMMUNE SYSTEM 330
TYPES OF IMMUNE CELLS 334
CHEMICAL MEDIATORS OF THE IMMUNE SYSTEM 349
KEY POINTS 386
ABBREVIATIONS 387
REFERENCES 389

CHAPTER 9 INFECTIOUS DISEASES 395
KEY POINTS 408
ABBREVIATIONS 409
REFERENCES 410

CHAPTER 10 VACCINES 412
INTRODUCTION 412
VIRAL VECTORS 414
CANCER VACCINES 415
VACCINES FROM DEAD OR INACTIVE ORGANISMS OR VIRUSES 416
CHILDHOOD IMMUNIZATIONS 417

FASTER WAYS TO MAKE VACCINES 422
CLASSIFYING VIRUSES 423
FLU (INFLUENZA) VACCINES 423
MMR VACCINE THE MMR 424
VARICELLA VACCINE 425
HEPATITIS A VACCINES 425
DTAP VACCINE 425
MCV4 VACCINE 426
MENINGITIS VACCINES 426
HUMAN PAPILLOMA VIRUS VACCINE 426
RISKS TO PHARMACEUTICAL COMPANIES 427
EFFORT TO DEVELOP NEW VACCINES 428
DISCOVERING ANTIGENS AND EVALUATING CELL-MEDIATED IMMUNE RESPONSES 429
ADVANCES IN ANALYZING IMMUNE RESPONSES 430
KEY POINTS 431
ABBREVIATIONS 431
REFERENCES 432

CHAPTER 11 PREVENTING DISEASES BY PROPER NUTRITION 435
NUTRITION 435
LIMITS TO USA RECOMMENDATIONS 439
RISKS IN EATING MASS-PRODUCED MEAT 439
FISH AND SEAFOOD 442
OTHER SOURCES OF OMEGA-3 AND POLYUNSATURATED FATS 444
SOYBEANS AND SOY PRODUCTS 444
TURMERIC 445
GINGER ROOT 446
ANTIOXIDANTS IN FRUITS AND VEGETABLES 446
FIGHTING STARVATION AND MALNUTRITION 447
GREEN REVOLUTION 448
POLLUTION, SOIL CONTAMINATION, ECOLOGICAL RISKS AND HUMAN HEALTH 449
CHEMICAL COMPOSITION OF SOIL AND THE CHANGES INVOLVED IN THE PRODUCTION OF CROPS AND LIVESTOCK 450
GENETICALLY-MODIFIED ORGANISMS (GMOS) 450
NUTRIENTS IN FOODS 452
DIETARY SUPPLEMENTS 456
BREAST FEEDING 457
VITAMINS 458
TOXICITY OF POORLY CHELATED IRON 467
HAZARDOUS DIETARY SUPPLEMENTS 468
SOME OF THE MOST IMPORTANT AND POPULAR DIETARY SUPPLEMENTS 469
KEY POINTS 482
ABBREVIATIONS 484
REFERENCES 485

CHAPTER 12 NEW PROBLEMS AND SOLUTIONS 494
EMERGENT PROBLEMS 494
GLOBAL CLIMATE CHANGE 496
BIOTECHNOLOGY-BASED SOLUTIONS 497
NANOTECHNOLOGY 501
P4 MEDICINE 504

STEM CELL TECHNOLOGY 505
SHORTAGE OF MEDICINES 508
TESTING FOR PROSTATE SPECIFIC ANTIGEN 509
OTHER IMPORTANT RECENT DISCOVERIES 510
RECENTLY APPROVED DRUGS 511
KEY POINTS 526
ABBREVIATIONS 528
REFERENCES 530

CHAPTER 13 COMMUNICATION AND SIGNALING IN MEDICINAL CHEMISTRY 538
INTRODUCTION 538
G PROTEIN-COUPLED RECEPTORS 543
PROTEIN KINASES 546
ABBREVIATIONS 546
REFERENCES 550

CHAPTER 14 SYSTEMS THINKING IN MEDICINAL CHEMISTRY 552
SYSTEMS BIOLOGY 552
EMERGENT PROPERTIES 556
SYSTEMS THINKING 561
SINLE CELL TECHNOLOGIES 562
AUTOPOIESIS, ALLOSTASIS AND ATTRACTORS 566
GAIA 574
NETWORKS 576
NETWORKS IN AGING AS WELL AS NEURODEGENERATIVE AND PSYCHIATRIC DISEASES 585
NETWORK ANALYSIS OF MOTHER'S MILK 587
CONCLUSION 588
KEY POINTS 588
ABBREVIATIONS 590
REFERENCES 590

APPENDIX 594

SUBJECT INDEX 663

FOREWORD

As a practicing physician, I found this third edition to be very up-to-date, interesting and useful. It would be an excellent text book for the second semester in the standard two-semester course taught at most pharmacy schools. I was especially impressed with the first chapter on predictive, preventive, personalized and participatory (P4) medicine. It epitomizes the fusion of traditional and western medicine. That is, mathematics, the foundation of reductionist thinking, is used to quantify huge datasets from patients, while physicists, chemists, biologists and engineers develop the analytical tools needed to generate the data. All of this can be linked through the internet and used in mobile healthcare applications. Also, the book concepts and metabolic processes for which there was limited knowledge or was completely unknown when I was a medical student. The information presented provides undergraduate, medical and pharmacy students with useful information about the indications for and applications of modern medicinal chemistry. It will also prepare currently licensed physicians prepare for Board certification and recertification. Many of the old questions may have new answers. I also found the book to be very helpful in describing medicines that I currently prescribe to patients and new drugs that are being developed. On frequent occasions, a patient will ask, “Why aren’t doctors doing more to find cures for common diseases”. The information in this book provides useful answers. I am also frequently asked questions about nutrition, dietary supplements and environmental toxins. The information about these subjects was written in clear, simple language that most people can understand. For example, I am frequently asked if it is beneficial to take the popular supplement, açaí, to help lose weight. Not being from Brazil, I didn’t know anything about it. This book talks about how açaí is 50% fat, as triglycerides. It is an excellent source of calories and antioxidants for undernourished natives and highly competitive athletes who need more calories. Taking açaí will actually make you gain weight. So, the book is very readable and has a multi-disciplinary approach. It teaches the kind of things that I would like to see medical and pharmacy students learn and could even be useful to lay people.

Mark D. Pilley
M.D. P.O. Box 241723 Omaha, NE 68124-3135
U.S.A

PREFACE

This book was written as a textbook for the second semester in a two-semester a course in medicinal chemistry that is taught in most pharmacy schools. It is preceded by the first edition, which was written for a one semester course and the second edition, which is for the first semester in a two semester course. They can be used in standard courses for pharmacy students and for students who are trying to get into medical, dental, pharmacy or graduate school. Moreover, people working in the pharmaceutical industry and doctors preparing for Medical Board Exams will also find it useful. The second edition discussed the fusion of traditional and western medicine and between systems thinking and reductionist thinking. This third edition contains chapters on personalized medicine and targeted drug discovery as well as the endocrine system that were not in the first edition. Unlike chapters in older books on medicinal chemistry, the chapter on the endocrine system talks about the alimentary tract and adipose tissues, which are now known to be secrete hormones. The importance of environmental toxins in autoimmune diseases is discussed. Practical advice is presented, especially when it helps illustrate an interdisciplinary approach and unexpected connections. The role of environmental toxins, such as bisphenol A (BPA) and perfluorooctanoic acid (PFOAA) in autoimmune diseases is discussed. Also, there are many updates based on research that was published since the first edition. New drugs have been approved and personalized medicine has benefited from next generation DNA sequencing methods. Also, three-dimensional printing was used to make a bioresorbable tracheal splint for an infant who was critically ill. So, advances in genomics, medical imaging, 3-D printing and regenerative medicine, along with increased computational power and the advent of mobile and wireless capabilities are allowing patients to be treated and monitored in ways that better meet their individual needs. There are also descriptions of the basic science behind cancer, heart disease, metabolic syndrome, infectious diseases, inflammation, reproductive medicine, the biology of information flow, the nervous system, immune network, vaccines, autopoiesis, systems biology and network theory. Finally, this and the topics discussed in it should not be taken as reflecting FDA policy or regulations.

CONFLICT OF INTEREST

The author confirms that this ebook contents have no conflict of interest.

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Declared none.

Robert E. Smith
Park University,
Parkville,
USA,
E-mail: Robert.Smith05@park.edu

DEDICATION

This book is dedicated to my wife, Dee.

I also want to thank the staff of Bentham Science for their tremendous help and support.

CHAPTER 1

Personalized Medicinal Chemistry

Abstract: Perhaps nothing epitomizes the fusion of traditional and western medicine more than predictive, preventive, personalized and participatory (P4) medicine. It takes not just a holistic but also a quantitative and mathematical approach to practicing medicine. Personalized medicine is designed for the specific genetic, epigenetic and environmental properties of patients and their diseased cells. Diagnoses, treatments and cures are improving for diseases caused by a single gene (Mendelian). As the costs of genotyping with microarrays and complete DNA sequencing continue to drop, new collaborative projects become possible. Biomarkers are being discovered through advanced genomic, proteomic, metabolomic and imaging technologies. This has a very high priority because they can improve the diagnosis of a disease, define subsets of patients and use appropriate therapies for them. Clinical trials are being modernized by automation and improved data management. Instead of just making the medicine specific for the DNA that a person is born with, it can be made specific for the mutated DNA that is in a type of cancer or other disease. This is being done by developing monoclonal antibodies, which will bind to receptors that are specific for a particular type of cancer. Some of them are even parts of FDA-approved medications. Most can't kill cells by themselves, but they can still bind to cancer-specific antigens and deliver drugs that are covalently attached to the monoclonal antibody. Even treatments for diseases that are caused by many factors (genetic and environmental) are benefiting from P4 medicine.

Keywords: Avastin®, Biomarkers, Campath®, Erbitux®, Gene chips, Herceptin®, Metabolome, Next generation sequencing, Personalized medicine, Rituxan®, Vectibix®.

INTRODUCTION

Perhaps nothing epitomizes the fusion of traditional and western medicine more than predictive, preventive, personalized and participatory (P4) medicine [1]. "It takes not just a holistic but also a quantitative and mathematical approach to practicing medicine. At the same time, systems medicine emphasizes prevention and individual participation in one's own health care. It recognizes the important

Robert E. Smith

human need for patients and care givers to be actively involved in preventing and curing their diseases. At the same time, mathematics, the foundation of reductionist thinking, is used to quantify huge datasets from patients, while physicists, chemists, biologists and engineers develop the analytical tools needed to generate the data. All of this can be linked through the internet and used in mobile healthcare applications" [1]. So, systems medicine is "the application of systems biology to the study of human disease" [1]. It can use data about biomarkers from many people and many different tissues in an individual to help everyone work with their physicians to make their own medical decisions.

Personalized medicine has been defined as, "the ability to customize medicine using molecular information to more accurately understand disease patterns and diagnose disease, as well as to tailor preventive and therapeutic intervention more effectively with fewer side effects" [2]. "It includes not only prescribing medicines, but also maintaining the mental and physical well-being of the patient and care givers. Pre-emptive genome-based testing of adults and children in personalized healthcare is becoming very helpful, especially when studying diseases with Mendelian inheritance. Diagnostic tests are now available for over 2000 Mendelian conditions. These tests are changing the paradigms for screening and diagnosing rare conditions. Personalized medicine can help identify patients who are more susceptible to certain diseases or disease-related symptoms or are pre-symptomatic. It will identify patients who will respond to preventive treatments differently or whose diseases or symptoms may progress differently when compared with others in the general population. Just as important, personalized medicine engages patients and helps them prevent diseases, decide treatments and monitor recovery. As we continue to personalize healthcare, the public is expressing their desire to participate actively in healthcare decision-making that is based on analyzing their genomes" [2].

So, personalized medicine "tailors medical treatment to the individual characteristics, needs and preferences of each patient" [3]. Actually, it has been used for over 100 years to analyze blood types, to ensure that transfusions don't cause hemolytic reactions. Also, over 50 years ago, the genetic basis for the selective toxicities of fava beans and an antimalarial drug (primaquine) was discovered. It is a deficiency in the enzyme glucose-6-phosphate dehydrogenase

(G6PD) that is important in metabolism. Then, in 1977, different isozymes of cytochrome P450 2D6 (CYP450 2D6) were found to cause the effects of the anti-hypertensive drug debrisoquine to be exaggerated and last longer than in others. So, genetic differences can cause different pharmacokinetic parameters, such as area under the curve, or AUC. Pharmacogenomics is the "study of how variations of DNA and RNA characteristics affect responses to drugs. It has been a crucial part of personalized medicine for decades" [3].

The goal is to prescribe different drugs and medical devices for people with different types of nutrition, environment, genes, mRNA, miRNA, epigenetics and/or proteins. Such treatments are designed for the patient's specific anatomy (size), physiology and environment (home, hospital, ICU). Diagnostic devices can monitor vital signs, blood glucose, oxygen or other small molecules. They can perform electroencephalography (EEG) or electrocardiography (ECG or EKG) and do diagnostic imaging. Some can even determine part or all of the genome, epigenome, transcriptome, proteome and metabolome of the patient and/or his or her diseased cells. Also, the patient's blood or tissues can be analyzed for different types of enzymes (isozymes, like CYPs) that catalyze reactions that can metabolize drugs differently and affect their bioavailability, or ability to bind to different receptors. Such an approach led to the development and rapid approval of tratuzumab, or Herceptin®, for treating and curing patients who have the HER-2 gene that is involved in many cancer signaling pathways. More recently, it led to four anticancer drugs being approved by the FDA "for use in patients who have specific genetic characteristics that can be identified by a companion diagnostic test" [3]. "Individualized medical devices are being made, too. Three-dimensional printing was used to make a bioresorbable tracheal splint for an infant who was critically ill. Furthermore, research on induced pluripotent stem cells (iPSCs) may lead to people being able to use their own cells to biosynthesize their own organs when they need a transplant. So, advances in genomics, medical imaging, 3-D printing and regenerative medicine, along with increased computational power and the advent of mobile and wireless capabilities, are allowing patients to be treated and monitored in ways that better meet their individual needs" [3].

There are many other examples of personalized medical devices [3]. "A customized tinnitus masker tailors audio signals to suit the patient's hearing

CHAPTER 2

Biology of Inflammation

Abstract: Inflammation can be a cause or a symptom of many diseases. When controlled, it is also an important part of maintaining good health. Reactive oxygen substances (ROS) are produced as part of normal, healthy aerobic metabolism, such as electron transport in the mitochondria of cells. Many foods, spices, herbs and dietary supplements contain antioxidants that can destroy ROS and help to prevent diseases. Some important dietary antioxidants include vitamins A and E, oleic acid, poly-unsaturated fats, omega-3 fats, resveratrol and polyphenols. Inflammation is a significant factor in many diseases, including arthritis, cancer, diabetes, heart disease, stroke, Alzheimer´s disease, hormonal diseases, osteoporosis, inflammatory bowel disease, pelvic inflammatory disease, and many others. Smoldering inflammation is a relatively low level of inflammation that occurs in obesity, type-2 diabetes, asthma, and atherosclerosis. In many cases, these diseases of inflammation can be prevented by avoiding obesity, trans fats and saturated fats that are in the typical fast food diet that many people in the USA consume. Instead, unsaturated fats are much better. Omega-3 fats can be taken as dietary supplements such as fish oil and flaxseed oil. They are also present in fatty fish, such as salmon. Omega-3 fats are also very important in the brain, where they play an important role in cognitive function and behavior. Inflammation plays an important role in all stages of atherosclerosis and cardiovascular disease. Inflammation is also an important factor in stroke

Keywords: Arthritis, Alzheimer´s disease, Cancer, Heart disease, Inflammation, Omega-3 fats, ROS, Saturated fats, Stroke, Trans fats.

Inflammation is also a part of traditional and western medicine. Infusions of willow bark were used by Native Americans to treat headaches, fever and overall inflammation. Unfortunately, the acidity of salicylic acid caused severe stomach problems in many people. While working in the lab of Adolf von Baeyer, Felix Hoffmann acetylated the carboxylic acid to make acetylsalicylic acid, or aspirin, thus reducing this harmful side effect.

Inflammation is also an area that has been misunderstood. For many years, the U.S. Department of Agriculture (USDA) maintained a website that listed the

Robert E. Smith

antioxidant potential of many foods and spices. This information was used in advertisements to help sell many products. One fruit, açaí, is still advertised as being the food with the highest antioxidant capacity. However, a few years ago, the USDA removed the data from the website because there is no evidence that consuming large amounts of antioxidants have little or no preventive or therapeutic value. Still, smoldering inflammation is known to be a cause of many diseases.

So, let us look at the underlying cause of many diseases – inflammation, along with some of the enzymes, oxidizing substances and antioxidants that affect it. When controlled properly, inflammation is an important part of maintaining good health. To get energy, human cells contain mitochondria, which make proinflammatory free radicals and reactive oxygen substances (ROS) as by-products of the TCA cycle and oxidative phosphorylation. Other subcellular organelles, called peroxisomes, oxidize fatty acids that have more than eight carbons and produce H_2O_2, which is broken down by the enzyme called catalase. Before it is broken down, H_2O_2 can oxidize compounds such as phenols, aldehydes and alcohols. Also, it can act as a second messenger that is produced in response to extracellular stimuli, and can regulate various biological processes.

Also, when disease-causing (pathogenic) microorganisms invade the body, immune cells kill the microbes by causing oxidative damage and inflammation. Although there is some collateral damage to the surrounding healthy cells and tissues, this does get repaired in healthy people. However, when the immune system is overactive, it can incorrectly identify environmental chemicals, foods and even one's own cells as foreign and mount a potentially fatal autoimmune response or allergic reaction. So, inflammation, like so much else, must be carefully controlled. Although pathogenic bacteria can cause inflammation and disease, remember that there are non-pathogenic bacteria that are essential for healthy human life. This includes *Bifidobacterium* and *Bacteriodes*, which help the immune system protect against the development of inflammatory diseases. They do this by helping to digest fermentable dietary fiber.

One definition of inflammation is that it occurs when parts of the body become red, warm, swollen, and damaged. This can happen when the immune system

responds to foreign materials, irritation, bone or nerve damage, infection by microorganisms, and ischemia (lack of blood flow), followed by reperfusion. Inflammation is caused by the production of reactive oxygen species (or substances) and other chemicals, such as histamine, pro-inflammatory proteins (cytokines) and eicosanoids [1]. Reactive oxygen substances (ROS) are produced as part of normal, healthy aerobic metabolism, such as electron transport in the mitochondria of cells. Please note that much of the chemical literature uses the term reactive oxygen species (ROS), instead of reactive oxygen substances, but many biologists would consider this to be a misuse of the word species. When oxygen reacts with nutrients and metabolites, it produces ROS such as hydrogen peroxide, the superoxide anion, the hydroxyl radical and nitric oxide. Hydrogen peroxide (H_2O_2) is made in mitochondria as a byproduct of biochemical reactions that produce energy for cells. It can react with unchelated iron (Fe^{2+}) and copper (Cu^{2+}) to produce the superoxide anion (O_2^-), which can also be produced by the reaction catalyzed by NADPH oxidases in immune cells.

$$2\ O_2 + NADPH \rightarrow 2\ O_2^- + NADP^+ + H^+$$

The superoxide anion can then react with other molecules to produce other ROS. When a pathogenic organism enters the body, NADPH oxidase in phagocytes and T lymphocytes that originate in lymph nodes produce ROS which kill the invading organism.

NADPH oxidase also exists in other tissues and its activation can be harmful. For example, NADPH oxidase in the lungs can cause oxidative damage after cardiopulmonary bypass operations [2]. A chemical carcinogen, diethyl-nitrosamine, can activate a signaling pathway in liver Kupffer cells (a type of macrophage) that causes inflammation and tissue damage [3]. In the brain, there is an NADPH oxidase in glial cells that is responsible for oxidative damage after suffering from a stroke. This can be prevented in gerbils by giving them apocynin, an NADPH oxidase inhibitor from *Picrorhiza kurroa*, a native plant grown in the mountains of India, Nepal, Tibet, and Pakistan [4]. Inflammation is a hallmark of acute stroke. Proinflammatory cytokines are released into the blood and brain. The immune system is also adversely affected, so stroke patients are susceptible to infections. In order to prevent this, regulatory T-helper cells release the anti-

CHAPTER 3

Metabolic Syndrome, Diabetes, Heart Disease and Stroke

Abstract: Heart disease is the biggest killer in the world. Its major cause is obesity or metabolic syndrome, which can also lead to diabetes and stroke - the third leading killer (after cancer) and the most frequent cause of disability in the world. All of these involve imbalances in energy metabolism. Early symptoms of metabolic syndrome include excessive weight, high blood pressure, elevated blood glucose and elevated levels of lipids, especially low density lipoprotein (LDL). People who have one or more of these symptoms are at a higher risk of developing heart disease, stroke and type-2 diabetes. Childhood obesity is such a big problem that it will probably mean that this generation will be the first to have a shorter life expectancy than their parents. Ischemic strokes need to be treated as soon as possible, so it is very important to get a stroke victim to a hospital as soon as possible, so the blockage can be removed and blood can begin to flow properly. Drugs such as aspirin, clopidrogel and dipyridamole can be given to prevent the formation of more clots by preventing blood platelets from aggregating. If the patient can get to a hospital soon enough, tPA, or tissue plasminogen activator, can be given. When blood flow to the heart is interrupted, it causes a myocardial infarction, or heart attack. The most common cause is a blockage in the coronary artery that is usually caused by the rupture of an atherosclerotic plaque.

Keywords: Diabetes, Heart disease, Metabolic syndrome, Stroke, Tissue plasminogen activator, tPA.

Next, let us look at the biggest killer in the world, heart disease, along with its major cause, obesity and metabolic syndrome, which can also lead to diabetes and stroke, which is the third leading killer (after cancer) and the most frequent cause of disability in the world. All of these involve imbalances in energy metabolism. However, let us also remember that somewhere in the world a child dies every 5 seconds from malnutrition or starvation, as described by the UN Secretary General, Ban Ki-moon in a three-day summit on food security in Rome in Nov. 2009. That is, hunger kills 17,000 children daily, while people in the USA and

Robert E. Smith

many other countries over-eat and suffer the effects of obesity.

GLUCOSE AND ENERGY PRODUCTION

For a person to be healthy, it is important that he/she is able to convert food into needed energy. Dietary carbohydrates are converted to glucose, which is the primary fuel that provides energy to our cells (especially in the brain), and as a source of intermediates for the biosynthesis of other carbohydrates, as well as nucleic acids, fats, amino acids and proteins. Glucose homeostasis is maintained by several hormones, with insulin and glucagon being the most important. When the concentration of glucose in the blood rises in a healthy person, the β-cells of the pancreas secrete insulin, which inhibits hepatic synthesis of glucose and/or increases glucose uptake into the muscles, liver and adipose tissue. This causes blood glucose levels to decrease. Glucagon is secreted by the α-cells of the pancreas when the concentration of glucose in the blood is low. Glucagon has the opposite effect of insulin. It stimulates the liver to make more glucose by breaking down some of its stored glycogen.

Glucose can be broken down further by glycolysis to produce energy, or it can be converted into glucose-3-phosphate and then into phospholipids and/or triglycerides, depending on the needs of the cell. Triglycerides can be stored for later use, or hydrolyzed into glycerol and free fatty acids, which can be used for fuel. When energy is no longer needed, fatty acids can react with glycerol to form triglycerides, which store energy.

Dietary proteins are broken down into amino acids, which can be used to make human proteins and polypeptides. Carbohydrates, nucleic acids, fats and proteins are interconvertible. So, people on a low fat, high carbohydrate diet can still biosynthesize the fats that they need. Similarly, people on a low carbohydrate, high protein and fat diet can make all the carbohydrates that they need. Since our bodies are continuously breaking down and re-making their internal components, we need food to supply the raw materials. Also, we need energy to live, so our diets must provide molecules like glucose, which can be broken down and converted to energy. The energy balance is closely regulated. More than 700,000 kcal are ingested each year by most well-fed adults, and “body weight is kept

within a range of ± 1 kg, or an equivalent of 7000 kcal. That is, "the regulation of energy operates with an accuracy of about 99% [1].

So, glucose can be broken down by the metabolic pathway called glycolysis, which occurs in the cytosol. Under aerobic conditions, glycolysis makes pyruvic acid, or pyruvate, along with a coenzyme called NADH, and a high-energy molecule called adenosine triphosphate, or ATP. The overall reaction is:

$$C_6H_{12}O_6 + 2\ NAD^+ + 2\ ADP + 2\ H_2PO_4^- \rightarrow 2C_3H_4O_3 + 2\ NADH + 2H^+ + 2ATP + 2\ H_2O$$

where $C_6H_{12}O_6$ is glucose and $C_3H_4O_3$ is pyruvic acid, which exists as pyruvate at physiological pH of 7.3 – 7.4. The structure of pyruvic acid is shown in Fig. (**1**).

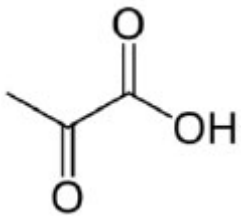

Fig. (1). Pyruvic acid, also written as $CH_3COCOOH$.

If there is not enough oxygen, as in over-worked muscle cells, pyruvate is converted to another carboxylic acid, lactic acid (lactate at pH 7.3). The lactate causes the burning sensation in over-worked muscles. Under anaerobic conditions, such as fermentation in yeast, the end product of glycolysis is ethanol. Also, remember that carboxylic acids, such as acetic acid, pyruvic acid and lactic acid are relatively weak acids and they lose one hydrogen ion (H^+) at pH 7.3, and become carboxylate anions, *i.e.*

$$CH_3COOH \rightleftharpoons CH_3COO^- + H^+ \ pK_a = 4.75 \text{ (Acetic acid)}$$

$$CH_3COCOOH \rightleftharpoons CH_3COCOO^- + H^+ \ pK_a = 2.39 \text{ (Pyruvic acid)}$$

$$CH_3CHOHCOOH \rightleftharpoons CH_3CHOHCOO^- + H^+ \ pK_a = 3.86 \text{ (Lactic acid)}$$

Once the pyruvate is formed in the cytosol of healthy cells, it goes to the mitochondria, where it is converted to acetyl-CoA, catalyzed by an enzyme called

CHAPTER 4

Biology of Cancer: Genetics, Biomarkers and Clinical Approaches

Abstract: Cancer is the rapid, unregulated and pathological growth (proliferation) of abnormal cells. Even when cancers occur in the same part of the body, they can be very different diseases. When tumors become malignant, their threat depends on their ability to modify surrounding cells to form new blood vessels (angiogenesis) and other supporting cells. The typical American diet that leads to obesity can make people more susceptible to cancer. The human papilloma virus, hepatitis B and T cell leukemia virus type 1 can cause cancer of the cervix, liver and leukocytes (leukemia). Tyrosine kinases regulate many cellular processes which can contribute to cancer development and progression. KRAS is the oncoprotein that is most commonly activated in human cancer [1]. *RAS* is one of the most commonly mutated genes in human cancers. Oncogenes code for oncoproteins, which are upregulated in cancer. Another important oncogene is *PI3K*, which codes for the enzyme PI3K (phosphoinositide 3-kinase). The enzyme PTEN (phosphatase and tensin homolog) catalyzes the opposite reaction, so it is a tumor suppressor and the gene coding for it is downregulated in cancer. Human epidermal growth factor (hEGF, or HER), vascular endothelial growth factor, or VEGF, and the PI3K/Akt/mTOR (mammalian target of rapamycin) survival pathway are all important therapeutic targets in many cancers [1]. Cancer stem cells could be good targets for new drugs that will prevent the recurrence and metastasis of tumors. Also, induced pluripotent stem cells could be used to screen drugs to see if they will be effective in treating each individual patient.

Keywords: Cancer, HER, Human papilloma virus, mTOR, RAS, PI3K, Tyrosine kinase, VEGF.

INTRODUCTION

Let us look at the group of diseases called cancer, the treatment of which often involves personalized medicine. The hallmarks of cancer are inflammation, chromosomal defects, genetic instability, escape from immunosurveillance, limitless proliferative potential, self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, sustained angiogenesis, tissue invasion

Robert E. Smith

and metastasis. As described in Chapter 2, smoldering inflammation can lead to cancer and other diseases. Reactive oxygen substances, such as the hydroxyl radical, produced by poorly liganded iron, can cause oxidative damage to DNA, proteins and lipids, affecting the genome, epigenome, proteome and lipidome. Inflammatory cytokines can be produced. Moreover, mutations accumulate as we age, eventually leading to the formation of new cell surface antigens. These things can change a tumor's interaction with the immune system, enabling it to escape immunosurveillance. Then, it develops limitless proliferative potential as it becomes self-sufficient in producing the growth signals it needs and becomes insensitive to antigrowth signals. Finally, a tumor becomes deadly when it builds new blood vessels and metastasizes into the lymph nodes and other organs.

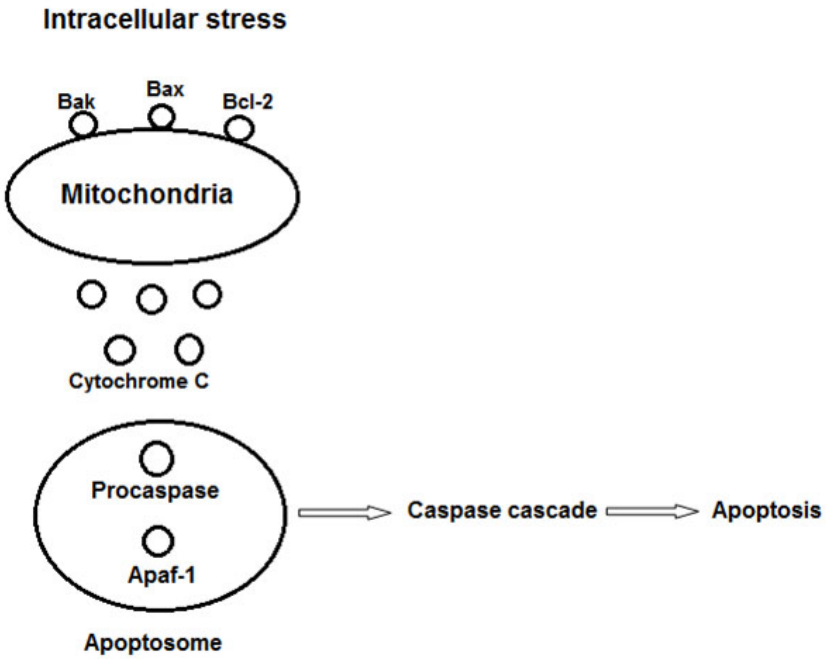

Fig. (1). Intrinsic pathway of apoptosis [1].

Most cells in our body are broken down and re-made. When a cell is damaged or just reaches the end of its normal life, it usually undergoes programmed cell death, also known as apoptosis. There is an intrinsic and an extrinsic pathway to apoptosis [1]. "The extrinsic pathway begins outside the cell, while the intrinsic

pathway begins inside the cell, as shown in Figs. (**1** and **2**). In both pathways, a class of cysteine proteases called caspases catalyzes reactions that dismantle dead and dying cells. When this apoptosis is disrupted, cancer can begin. Abnormal cells should die, but they don't. The mitochondria, which regulate apoptosis in healthy cells, become defective. Not only do they not initiate apoptosis, but their metabolism changes. Despite the ready availability of O_2, glycolysis occurs as if it was in an anaerobic environment and the end product is lactate, not pyruvate. This is called the Warburg effect, after the scientist who discovered it. At first, this was thought to be a cause of cancer, but we now know that it is an effect, or a symptom. Recent data has shown that the loss of the tumor suppressor SIRT6 may be the cause of the Warburg effect" [1].

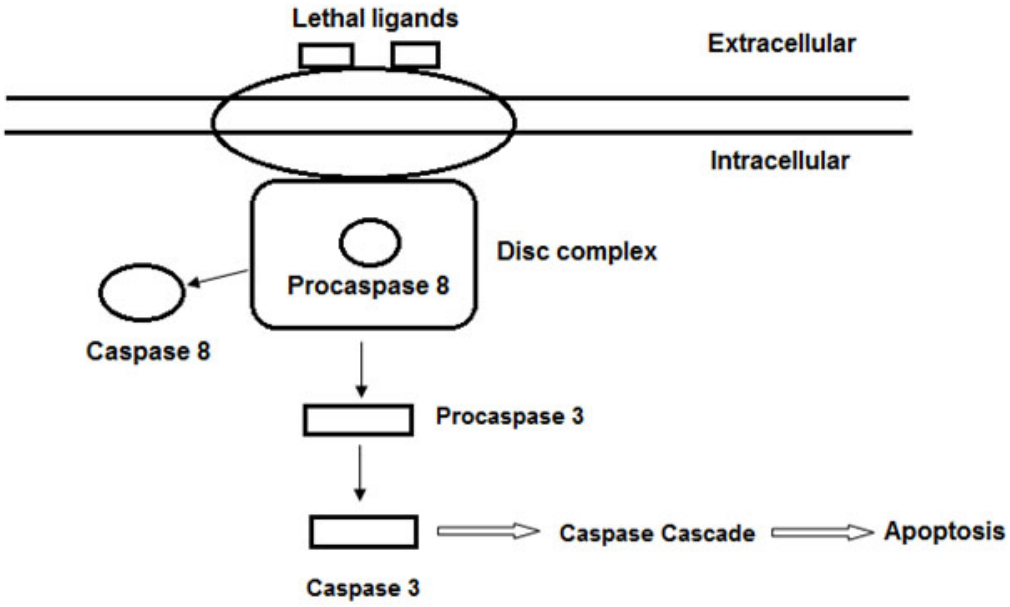

Fig. (2). Extrinsic pathway of apoptosis.

Unfortunately, there are many websites and books that promote pseudo-science and dangerous alternative cancer therapies. Some of them say that cancer can be cured if you can just get more oxygen into the cancer cells. One book (written by an accountant, not a scientist) even tells people with breast cancer to perfuse the breast with baking soda, or $NaHCO_3$, as if the oxygen in the HCO_3^- can magically

CHAPTER 5

Medicinal Chemistry and the Endocrine System

Abstract: The endocrine system consists of cells, glands and tissues that secrete hormones into the bloodstream that affect physiological and behavioral function and activities [1]. This is in contrast to the exocrine system that secretes substances into ducts. The hypothalamus connects the nervous and endocrine systems to each other through the pituitary gland, or hypophysis. It helps control body temperature, hunger, parenting and attachment behavior, thirst, fatigue, sleep, circadian rhythms and other activities of the autonomic nervous system. Darkness causes the pineal gland to secrete N-acetyl-5-methoxytryptamine, which is better known as melatonin. Melatonin is part of the system that regulates the sleep-wake cycle. It causes drowsiness and lowers the body temperature. The anterior lobe of the pituitary gland secretes growth hormone (GH), beta-endorphin, luteinizing hormone (LH), follicle stimulating hormone (FSH), melanocyte stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH) and prolactin (PRL). The posterior lobe stores vasopressin, also known as antidiuretic hormone (ADH) and oxytocin (OXT). The thyroid gland helps control how fast a body uses energy and makes proteins as well as influencing the sensitivity of the body to other hormones. It does this by producing T3 and T4, which are made from tyrosine and iodine. The stomach, duodenum, liver, pancreas and kidneys all secrete hormones. The kidneys secrete renin, erythropoietin, calcitrol and thrombopoietin. They regulate pH, electrolytes and blood pressure. The adrenal glands produce hormones in response to stress by synthesizing corticosteroids such as cortisol and catecholamines, such as adrenaline (epinephrine) and noradrenaline (norepinephrine). They also produce androgens in their innermost cortical layer. The adrenal glands affect kidney function by secreting aldosterone. The testes, ovarian follicle and corpus luteum are in the endocrine system, as are the placenta and uterus when a woman is pregnant. The testes secrete androgens (mostly testosterone), estradiol and inhibin. They stimulate or control the development and maintenance of male characteristics by binding to androgen receptors. This includes the activity of the male sex organs and development of male secondary sex characteristics. Androgens are also the original anabolic steroids and the precursor of all estrogens. The endocrine system also regulates the concentration of Ca^{2+}. The parathyroid gland secretes the parathyroid hormone (PTH), which stimulates Ca^{2+} release from bones, stimulates osteoclasts and Ca^{2+} reabsorption in the kidneys. Calcium regulation also occurs in the skin, which secretes the prehormone calcidiol (25-hydroxyvitamin D3), the inactive form of vitamin D. The major endocrine systems are the TRH-TSH-Y3/T4, the GnRH-

Robert E. Smith

LH/FSH-sex hormones, the CRH-ACTH-cortisol, the renin-angiotensin-aldosterone system and the leptin *vs* insulin system. The TRH-TSH-Y3/T4 system is also called [1].

Keywords: Adrenal, Endocrine system, Hypothalamus, kidneys, Parathyroid, Pituitary, Reproductive system, Thyroid.

As described in Chapter 3, adipose tissue is an important part of the endocrine and immune systems [1]. That is, the endocrine system consists of cells, glands and tissues that secrete hormones into the bloodstream to affect physiological and behavioral function and activities [1]. This includes metabolism, tissue function, sleep, mood, growth and development. On the other hand, the exocrine system secretes substances into ducts. Like the nervous system, the endocrine system sends and receives information in the form of biochemical messages. However, its effects are slower to get started and last longer than those of the nervous system. A series of glands secrete hormones. When several of them signal each other in sequence, they can be called an axis, as in the hypothalamic-pituitary-adrenal axis.

HYPOTHALAMUS

The hypothalamus is a small portion of the brain, located below the thalamus and above the brainstem [1]. “It connects the nervous and endocrine systems to each other through the pituitary gland, or hypophysis. It helps control body temperature, hunger, parenting and attachment behavior, thirst, fatigue, sleep, circadian rhythms and other activities of the autonomic nervous system. When stimulated by high amplitude oscillations (delta waves) from the thalamus or cortex in the brain, it secretes neurohormones that are often called releasing hormones, for they stimulate or inhibit the release of pituitary hormones. Secretion of GHRH and prolactin is stimulated, while thyroid releasing hormone (TRH) is inhibited. At the same time, it responds to many different signals, of internal and external origin. It responds to daylight, circadian and seasonal rhythms, odors, gonadal steroids, corticosteroids, autonomic input, stress, invading organisms, neural input from the heart, stomach and reproductive tract and biochemicals in the blood. This includes peptide hormones, leptin, gherlin, insulin, pituitary hormones, cytokines, glucose and osmolarity” [1]. So, let’s look closer at this amazing part of the brain and endocrine system.

The hypothalamus has distinct nuclei and other less distinct areas. In the hypothalamus, the axons of magnocellular neurosecretory cells in the paraventricular nucleus and the supraoptic nucleus contain oxytocin and vasopressin (antidiuretic hormone), and project into the posterior pituitary gland [1]. "Much smaller neurons of the paraventricular nucleus release corticotropin-releasing hormone (CRH) and other hormones into the hypophyseal portal system, where they diffuse to the anterior pituitary. The hypothalamus also secretes orexins (also called hypocretins), ghrelin, gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone (GHRH), somatostatin, and thyrotropin-releasing hormone (TRH), along with the non-peptide hormone, dopamine (which can also act as a neurotransmitter)" [1].

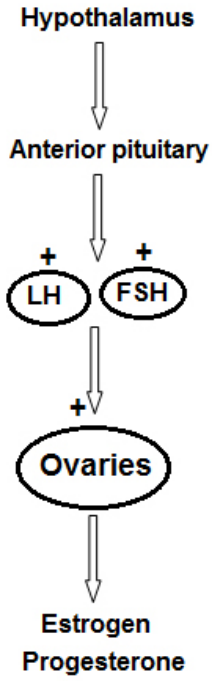

Fig. (1). Hypothalamic-adenohypophyseal (anterior pituitary) axis.

Along the hypothalamic-adenohypophyseal (anterior pituitary) axis (Fig. **1**), somatostatin is produced by the neuroendocrine cells of the periventricular nucleus. It inhibits the release of GH and TSH from the anterior pituitary [1].

CHAPTER 6

Reproductive Medicine, Osteoporosis

Abstract: The fertility cycle in women is controlled by a cascade of events, which are initiated by protein and steroid hormones. These hormones create signals between the hypothalamus, the pituitary gland and the ovaries. Oral contraceptives contain an estrogen-like drug, ethinyl estradiol. It is combined with any of a number of progestin derivatives. Progestin-only pills are available for women who are breast feeding and those who are not able to tolerate estrogens. There is also an emergency contraceptive to prevent pregnancy after unprotected intercourse, called Plan B. One form consists of two pills, each containing 0.75 mg of levonorgestrel. Mifepristone is a synthetic steroid that is used for the termination of pregnancy up to the 49th day of gestation. It has been tested as a morning after pill to prevent pregnancy when taken within 12 hours of unprotected intercourse. It is also used in combination with another drug called Gemeprost to terminate pregnancies between weeks 13 and 24. In the USA, levonorgestrel is the preferred emergency contraceptive. It can prevent a pregnancy up to 72 hrs after unprotected sex or contraceptive failure. Oxytocin and prostaglandin E_2 are also available to induce labor by stimulating uterine contractions. Some women take hormone replacement therapy, in which a low dose of one or more estrogens (conjugated equine estrogens) and a progestin are given. Another approach is to increase the consumption of soybeans and foods made from soybeans (such as soy milk).

Keywords: Gemeprost, Levonorgestrel, Mifepristone, Progestin, Prostaglandin E_2, Soy.

Reproductive medicine studies fertility, sexuality, reproduction and menopause. Studying these fields may lead one to embrace systems thinking, more than reductionist thinking. The blueprint of life includes more than just DNA. In the plant kingdom, the same DNA and chromosomes can make a plant male or a female, depending on the amount of light in the environment (the length of the light and dark cycle). In amphibians, the number of males and females depends on the environment. The instructions for life also include hormones and an immune system that seems to be able to predict the future. By the time we are three years

Robert E. Smith

old we are well immunized, and our immune cells are able to distinguish self from non-self. The body's white blood cells attack and destroy cells that are foreign, but they don't bother their own cells [1]. Then, as puberty begins, we start making new cells. Somehow, our immune system is able to recognize these new cells as being self, instead of non-self. Throughout life, the immune system is able to distinguish between harmful exogenous bacteria and helpful commensal bacteria. However, there are important gender differences. Women are more susceptible to autoimmune diseases, due partly to differences in gut bacteria, which help regulate sex hormone levels [1]. The composition of the gut bacteria diverges during the onset of puberty. The bacteria in males can help protect them from type-1 diabetes [1].

Also, the innate immune system produces interferon-ε (Ifn-ε), which protects the female reproductive tract from infection [2]. "It is produced constitutively in the epithelial cells. The innate immune system senses pathogens through pattern recognition receptors that induce cytokines such as type 1 interferons, which activate effector cells. All type 1 interferons protect against HSV-2 infection, but Ifn- ε is the one that protects against *Chlamydia* infection. So, it may be important in fighting this and other sexually transmitted diseases" [2]. Machines don't do these things, living autopoietic systems do.

A group of human autopoietic systems formed a not for profit organization, the American Society for Reproductive Medicine, or ASRM [3]. They publish scientific journals and other information for patients, doctors, and anyone interested in learning more. These include topics such as adoption, age and fertility, assisted reproductive technologies, ectopic pregnancy, endometriosis, infertility, laparoscopy and hysteroscopy, multiple pregnancies and birth, pelvic pain, and others [1]. The following describes some of the basics.

The sex steroids (estrogens, progestogens and androgens) play crucial roles in the development and selection of sex in the embryo. They help masculinize or feminize the brain at birth, develop secondary sexual characteristics and control reproduction and reproductive behavior in adults [1]. All three classes of sex steroids are present in males and females, but the plasma levels of estrogens and progestogens are higher in females, while androgens are higher in males.

Endogenous human estrogens include 17β-estradiol, estriol, estrone and their conjugates. Before menopause, 17β-estradiol is the predominant estrogen in the blood. The ovaries produce it and estrone, while estriol is made by 16α-hydroxylation of estrone and estradiol [1]. Estrone is elevated after menopause, where it is made in adipose tissue. As menopause begins, there is a decrease in estrogens, which can be treated with hormone replacement therapy (HRT). So, sex steroids are important at every stage of life, and survival of the species depends on them. They bind to estrogen and progesterone receptors. They interact with other proteins to affect DNA transcription.

All three estrogens exert their activities through α and/or β-estrogen receptors. The α receptor is located in the endometrium, ovary and breast cancer cells, while the β receptor is found bones, kidneys, lungs, endothelial tissues and other organs [1]. Estriol has the weakest affinity for either receptor, estrone binds mostly to the α receptor and 17β-estradiol has the highest binding affinity for both receptors [1]. Biological responses for the short-time elevation of estrogens are similar to long-term delivery of lower doses.

Progestogens like progesterone comprise the class of steroid hormones that have pro-gestational effects. They are pro-gestational. They help maintain gestation, or pregnancy. They are also precursors of other steroids. Progestrone is the major naturally occurring progestogen [1]. It is involved in embryogenesis, pregnancy and the menstrual cycle. It is produced in the adrenal glands and ovaries, by the corpus luteum. During pregnancy, it is also produced in the placenta. It is stored in adipose tissue.

Androgens are male hormones that bind to androgen receptors and control the development and maintenance of male characteristics. They are also known as anabolic steroids. They promote the enlargement of skeletal muscle cells. They are also the precursors of estrogens. The primary androgen is testosterone, but dihydrotestosterone (DHT) and androstenedione are also quite important in male development. DHT is a metabolite of testosterone. It is made in the skin and reproductive tissue. It binds to the androgen receptor tighter than testosterone. Later in life, DHT contributes to prostate growth, male balding and sebaceous gland activity. There are also 19-carbon androgens that are made in the adrenal

CHAPTER 7

The Nervous System

Abstract: The first year of life is critical in brain development, for the total brain volume doubles, as measured by MRI. This is when the brain is most susceptible to damage by genetic defects and environmental insults. It is also the time in which therapeutic intervention can have its maximum effect. A principal component of the nervous system is the neuron. Neurons are arranged in networks and circuits. The normal human brain has many local regions, or centers, and many pathways between them. The autonomic nervous system is organized into three divisions: the sympathetic, parasympathetic and enteric [1]. These maintenance activities are usually performed without conscious control or sensation. The sympathetic and parasympathetic nervous systems work to maintain a type of balance. They have opposite effects on the body. The sympathetic division is used in actions requiring quick responses. The parasympathetic division is used in actions that do not require immediate reaction [1]. Messages are sent to and from neurons in the form of primary messengers, called neurotransmitters. L-DOPA is used to treat Parkinson's disease, which affects about 1% of the population over 65. Alzheimer's disease (AD) is the most common neurodegenerative disease. Phenobarbital, carbamazepine, valproic acid and its sodium salt, gabapentin, ethosuximide, lamotrigrine, and tiagabine are anti-epileptics. Diazepam, buspirone, b-blockers, tricyclic antidepressants and monoamine oxidase inhibitors treat anxiety disorders. Currently the first-line treatment is either SSRIs or SNRIs. The four main classes of antidepressant drugs are MAOIs, TCAs, SSRIs and SNRIs.

Keywords: Alzheimer's disease, Autonomic nervous system, Neuron, Parkinson's disease.

INTRODUCTION

The nervous system can be studied using systems thinking. As mentioned before, one of the weaknesses of reductionist thinking is the inability to explain much of embryology, growth or development. The growth and development of the human brain and its cells from neural stem cells is a fascinating field [1]. Remember that stem cells have the same set of genes that differentiated cells have, but those

Robert E. Smith

genes are controlled differently in different cells. They are masters of autopoiesis. Moreover, the human nervous system is a network of molecules, ions, sub-cellular organelles, cells, tissues and organs. Chemical and electrical signals are transmitted from neuron to neuron in complex networks and circuits in the brain. This network and its circular organization are linked with other tissues and organs, including the endocrine system, digestive system, liver and immune system. As mentioned in Chapter 5, one example is the fibroblast growth factor FGF 21, which is a hepatokine (cytokine secreted by the liver) that acts as a global starvation signal to modulate fuel partitioning and metabolism as well as repress growth by acting on the nervous system [1]. It acts through its receptor in the brain, β-Klotho, to lower insulin, inhibit growth, alter light-dark cycle activity, increase systemic corticosterone levels and inhibit female fertility. It also suppresses the expression of the neuropeptide vasopressin in the suprachiasmatic nucleus (SCN) of the brain, which also expresses receptors for ghrelin and leptin [2]. It also contributes to neuroendocrine control of female reproduction by acting on the SCN in the hypothalamus to suppress ovulation during starvation [2].

Network analysis of neural systems in humans and other species show something called the small-world network phenomenon. That is, information can be transferred from one region to any other region by traversing only a few major white matter tracts [3]. So, any two neurons can communicate by the transmission of signals over just a few synapses. Networks consist of nodes or vertices, connected by line segments or edges. This will be discussed further in Appendix 2.

The human brain develops slower than the other organs, even though we are born with almost all the neurons that we will ever have. The first year of life is critical in brain development, for the total brain volume doubles, as measured by MRI [3]. This is when the brain is most susceptible to damage by genetic defects and environmental insults. It is also the time in which therapeutic intervention can have its maximum effect [3]. The brain continues to grow during the first two years of life, due to the growth and division of supporting cells (glial cells) in the white matter and there is a large increase in connections (synapses) between neurons in the gray matter. Glial cells are derived from myeloid precursors and migrate into the brain during development. Unlike the most of the rest of the

body, it is mostly just these glial cells that are being continuously being broken down and re-made in the brain [4, 5]. Most adult neurons do not undergo mitosis and are not regenerated when they die. Neurogenesis probably does not occur in most regions of the brain, but some data suggest that adult neurogenesis might occur in the neocortex, striatum, amygdala, hypothalamus and brainstem [6]. There is much more evidence that adult neurogenesis occurs in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus (which is involved in learning and memory) and the subventricular zone, or SVZ (in which neural stem cells reside) of the lateral ventricle [7]. Neural stem (or progenitor) cells can respond to external neural activity and differentiate into neurons [7]. This activity-dependent neurogenesis requires Ca^{2+} channels and receptors for the neurotransmitter *N*-methyl-D-aspartate (NMDA) [7]. It is called excitation-neurogenesis coupling [8]. "That is, neuronal stem cells respond to electrical signals from neighboring neurons by expressing appropriate genes and signaling pathways. This is mediated by GABA-mediated membrane depolarization, which causes an increase in intracellular Ca^{2+}. The excitation signal activates the transcription factor called NeuroD and promotes neurogenesis. Once the stem cells differentiate into neuroblasts and neurons, excitation by GABA helps the new neurons to be integrated as functional units. Moreover, neural stem cells called type 1 or radial glial-like (RGL) cells can respond to neural activity. RGLs maintain the adult neural stem cell pool in the hippocampus by remaining quiescent. The maintenance and activation of RGLs is controlled dynamically by experience and aging. RGLs that express the protein called nestin can be activated by GABA. The absence of functional $GABA_A$ receptors causes a rapid exit from quiescence and an increased production of RGLs. Interneurons in the stem cell niche that express the Ca^{2+}-binding protein parvalbumin are are a source of GABA. They are required to maintain RGLs. When GABA signaling is modulated, it affects the generation of more RGLs or causes them to remain quiescent, but not to differentiate. So, the adult brain continues to develop under the influence of electrical activity, while behavior and circuit activity control adult neurogenesis" [8].

Neurogenesis occurs throughout life in the SVZ. Neurons that are generated there migrate to the olfactory bulb, where they become interneurons [7]. Even though

CHAPTER 8

The Immune System and Immune Network

Abstract: The immune system recognizes and defends us against internal threats caused by invading organisms and pathogens. The innate immune system recognizes bacteria, fungi and other organisms, breaks them down, identifies a characteristic protein on them (an antigen) and attaches it to the surface of specific cells, which present it to the adaptive immune system for destruction. The adaptive or acquired immune system is activated after being stimulated by the innate system. The adaptive immune response is initiated by specific interactions between antigen-bound, mature dendritic cells and naïve $CD4^+$ T cells in the lymph nodes. The adaptive or acquired immune system acts once it is stimulated by the innate system. The five families of immune cells are: phagocytes, granulocytes, natural killer (NK) cells, lymphocytic T-cells and lymphocytic B-cells. The four major classes of immune system mediators are chemotactic agents, cytokines, C-reactive protein and antibodies. A fifth class of immune network mediators are the small molecules, including neurotransmitters, such as L-DOPA and catecholamines. Risk factors for autoimmune diseases include exposure to man-made chemicals. Benlysta (belimumab) is approved for treating lupus erythematosus. AIDS is caused by the retrovirus HIV. Currently, a mixture, or cocktail of antiretroviral drugs are given in what is often called highly active antiretroviral therapy, or HAART. Microbes in the intestines and lungs (acquired from the environment) keep rare invariant natural killer immune cells from triggering autoimmune diseases.

Keywords: Adaptive, Autoimmune diseases, HAART, HIV, Immune system, Innate.

Just as the nervous system can be studied by systems thinking so can the immune system or immune network. In fact, the immune and nervous systems are closely linked. Some of the molecules that are produced by our immature immune systems help regulate the growth and development of our nervous systems. There are other molecules that are used to communicate information in both the immune and nervous systems. Both systems are used in making decisions. The brain helps us recognize and defend ourselves against external threats, while the immune

Robert E. Smith

system recognizes and defends us against internal threats caused by invading organisms and pathogens. Regular cardiovascular exercise (endurance training) and proper nutrition are important for the nervous and immune systems. Both are essential in helping to establish the boundaries between self and the environment and the difference between food and poison. It is essential that we can distinguish between self and non-self. This is important because we are constantly being exposed to many man-made chemicals, viruses and organisms that are potentially very dangerous. From the outside of our skin to the inside of our bodies, we have many ways to defend ourselves. Similarly, all organisms have defenses. Both invertebrates and vertebrates have an innate immune system, but only vertebrates have an acquired (or adaptive) immune system. In fact, it is often described as an immune network.

Our first line of defense is composed of physical and chemical barriers, such as antimicrobial peptides and enzymes (like lysozyme) that are secreted by saliva, tears, the respiratory tract and the skin (a physical barrier). In the gut, commensurate (or commensal) bacteria help prevent infection by pathogenic bacteria. The ecosystem that comprises the human organism co-evolved with commensurate bacteria that have established a niche for themselves, in which they have a competitive advantage over other bacteria. The highest density of commensurate bacteria in the human body is found in the gastrointestinal tract [1]. There is a mucus tract that covers it and influences the function of antigen presenting cells (APCs) and epithelial cells so that our dendritic cells (DCs) can tolerate food and commensurate bacterial antigens [1]. This mucus tract contains glycoproteins called mucins, including MUC2. It prevents inflammation by forming a non-attached outer mucus layer that is inhabited by bacteria. MUC2 also forms an inner mucus layer that adheres to intestinal epithelial cells. It mitigates inflammatory responses to DCs by generating signals that make them tolerant to antigens [2]. DCs lie just beneath the epithelial layer of cells and presents foreign antigens which we should not try to tolerate to other cells in the immune system.

When these first lines of defense fail to block pathogenic bacteria or other immunogens, the innate and adaptive immune systems are activated. Both use white blood cells (leukocytes), which are a diverse group of cell types that

mediate the body's immune response. They circulate through the blood and lymphatic system and are recruited to sites of tissue damage and infection [1].

Acute inflammation is made up of antibodies and humoral factors in the cell-free blood serum and other bodily fluids, once known as humors. This includes the complement system, coagulation system, iron-binding proteins (lactoferrin and transferrin), interferons, lysozyme and a protein called interleukin-1, or IL-1. Antibodies are made in B cells, which are lymphocytes that are made in the bone marrow [1]. "The innate immune system recognizes pathogen-associated molecular patterns (PAMPs), which include double-stranded RNA, lipo-polysachharides and other molecules that are common in viruses, bacteria and fungi, but not in healthy human cells. The innate immune system senses the presence of microbial pathogens by detecting cytoplasmic DNA. However, erroneous detection of dinucleotides can help cause some autoimmune diseases" [1].

The innate immune system also recognizes damage- or danger-associated molecular patterns (DAMPs) released from damaged cells, such as uric acid crystals or ATP [1]. "It protects the host from infection by other organisms in a relatively non-specific way. The human innate immune system recruits immune cells to the site of infection, activates the complement cascade, identifies and removes foreign substances and activates the adaptive immune system through antigen presentation. That is, the innate immune system recognizes bacteria, fungi and other organisms, breaks them down, identifies a characteristic protein on them (an antigen) and attaches it to the surface of specific cells, which present it to the adaptive immune system for destruction. The innate immune system does not have a memory and does not offer specific resistance against organisms that have invaded the host in the past. For this, the adaptive immune system is needed. It is activated by the innate immune system. It is made of many parts" [1].

Invading cells are killed by phagocytosis using a subgroup of leukocytes that circulate in the blood as monocytes [3]. "They are converted into macrophages, which enter tissues during inflammation. There is much heterogeneity in phenotype, homeostatic turnover and function when they are present in different tissues. Dendritic cells (DCs) are a distinct lineage of mononuclear phagocytes,

CHAPTER 9

Infectious Diseases

Abstract: Infectious diseases can be caused by worms, protozoa, fungi, bacteria, viruses and even proteins (prions). Organisms, viruses and prions can be classified by their infectivity, or their ability to enter, survive and multiply in a host. There are seven classes of viruses, based on their DNA or RNA. By number, 90% of the cells in the human body are bacteria. Even though our lives depend on symbiotic bacteria, it is important that they stay in their proper places in our human bodies, or ecosystems. By the mid-1980s strains of *S. aureus* emerged which were resistant to common antibiotics. Multicellular parasites include four species of *Schistosoma*, a flatworm that causes schistosomiasis, which is second in importance only to malaria, with hundreds of millions infected worldwide. In addition to schistosomiasis, helminths can cause ascariasis, dracunculiasis, elephantiasis, hookworm, lymphatic filiaruasis, oncho-cersiasis, and trichuriasis.

Keywords: Bacteria, Fungi, Infectious diseases, Mycobacterium , *S. aureus*, Tuberculosis, Viruses.

Next, let us look at the biggest killers throughout most of human history – infectious diseases. They can be caused by parasitic worms, fungi, protozoa, bacteria, viruses and even infectious proteins, called prions. They can exist in a self-propagating state that is biologically accessible, but rarely form spontaneously [1]. "They also can replicate themselves by acting on their non-prion substrate protein, spread to naive hosts and find new substrate pools for replication. Finally, prions also cause phenotypic changes in the host. In mammals, they propagate after post-translational conversion of the host's normal, detergent-soluble, protease sensitive PrP (PrP^{C} or PrP-sen) to a less soluble and more proteinase-K resistant state (PrP^{RES} or PrP^{Sc}). The most infectious particle per unit protein is an oligomer containing 12-24 PrP monomers. The prototypical prion PrP^{Sc} causes Mad Cow disease, also known as bovine spongiform encephalopathy (SGE). It is also called the SGE prion. It also causes Creuzfeldt-Jakob disease in humans. Once PrP^{RES} is made, it can accumulate on the cell

Robert E. Smith

surface, in intracellular lysosomal vesicles, or in extracellular deposits such as amyloid plaques" [1].

Infectious diseases are usually contagious. They can be transferred from one person or species to another. Organisms, viruses and prions can be classified by their infectivity, or their ability to enter, survive and multiply in a host. Most biologists do not consider viruses to be alive, and none consider prions to be alive. Prions are proteins, or pieces of proteins that can cause mad Cow disease and Creuzfeld-Jakob disease. The natural, healthy prion, PrP^{C}, is soluble, but anchored to cell membranes by glycophosphatidyl inositol (GPI) [1]. It is coded by the *Prnp* gene [2]. The function of PrP^{C} is not well known, but it may act as a copper-dependent antioxidant. It is also involved in maintaining the brain's white matter, regulating the innate immune system, and forming new neurons. It may also function in long term memory, or the ability to remember things that happened hours, days, months, years or decades earlier. There are also two mammalian PrP paralogs, Doppel and Shadoo [2]. Normally, Doppel is mostly expressed in testes, but its ectopic expression can cause neurodegeneration in the central nervous system (CNS). Shadoo is expressed in the CNS. Both Doppel and Shadoo share neuroprotective properties [2].

The infectious form of PrP, PrP^{Sc}, is able to convert PrP^{C} proteins into an infectious form by post-translational modifications that make them less soluble and more resistant to degradation catalyzed by proteinase-K. The modified, pathogenic prions also lose their N-linked glycans and GPI anchor to the cell membrane. Aggregations of these abnormal forms can make amyloid fibers. Similar pathogenic amyloids, amyloid beta, or Aβ, form plaques and cause severe brain damage in Alzheimer's disease. The exact amyloid form of Aβ that may help cause Alzheimer's disease remains a matter of debate, but recent evidence suggests that smaller sub-amyloid Aβ oligomers are being more neurotoxic [1].

The next in size are viruses, which are more than just proteins, but still, they don't make their own surface coat or internal components – their hosts make them. Viruses are not cells, nor are they made up of cells. They don't have their own metabolism, even though they do evolve. Viruses use enzymes and structures within their host to make their surface or capsid, and to make copies of

themselves. Most biologists don't consider viruses to be alive, but almost all talk about ways to kill them. Though not truly alive, viruses can infect their hosts and cause potentially fatal diseases. It is also quite likely that the human genome contains many remnants of viruses, in the form of retrotransposons. Viruses can also mutate and form new strains that can infect different species. This has happened when bird flu and swine flu infected people. This was alarming, because nobody was immune to the new strain, and the annual flu shot did not protect it, although recent research may develop better vaccines. Fortunately, the most recent strain of the flu virus had relatively low virulence, but it could mutate into a new strain that is more virulent. However, one should remember that even the different strains of influenza virus that have been around for decades kill about 36,000 people in the USA each year.

Even though viruses are not alive, they can be classified the same way as are plants and animals. They can be assigned to an order, family, subfamily, genus and species. In another classification system, viruses are classified by the way that their mRNA is made. The seven classes of viruses are: dsDNA, ssDNA, dsRNA, (+)-sense ssRNA, (-) -sense ssRNA, RNA reverse transcribing and DNA reverse transcribing. Viruses can also be classified by different types, subtypes and strains. For example, the influenza virus is divided into Types A, B and C. The natural or most common hosts for Type A viruses are birds. However, Type A viruses can also infect humans and other animals. Type B viruses are normally only found in humans. Although they have caused epidemics, they have not caused pandemics. Type C viruses cause mild illnesses and do not cause epidemics or pandemics. Types B and C are not further divided into subtypes. Because they can be so deadly, Type A influenza viruses are classified further. They have different proteins on their surfaces. There are 15 different subtypes with different hemagglutanin (HA) proteins and nine different neuraminidase (NA) proteins. So, the H_1N_1 virus has HA protein number 1 and NA protein number 1 on its surface. Especially dangerous virus subtypes can also be classified further into different strains, based on differences in their DNA or RNA, which can be caused by mutations. The recent strain of H_1N_1 swine virus that emerged in Mexico, in April 2009 has "genes" (RNA) from human and avian influenza, as well as swine. Even though most people infected in the USA with

CHAPTER 10

Vaccines

Abstract: An extremely important part of disease prevention is vaccination, which improves the immune response to a particular disease. Vaccines save lives and prevent deadly diseases that used to take millions of lives, especially the lives of infants. Vaccines can be made from dead or inactive organisms or viruses. Vaccines can also contain "live" attenuated viruses. The tetanus and diphtheria vaccines contain inactivated toxic compounds. Children should be vaccinated against hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, polio, *Pneumococcus*, measles, mumps, rubella, rotavirus, human papilloma virus (HPV), Meningococcus, *Orthomyxoviridae* (flu virus) and varicella (chicken pox).

Keywords: (HPV), Chicken pox, Diphtheria, Flu virus, Hepatitis A, Hepatitis B, Human papilloma virus, Measles, Meningococcus, Mumps, Orthomyxoviridae, Pertussis, Pneumococcus, Polio, Rotavirus, Rubella, Tetanus, Varicella, Vaccination.

INTRODUCTION

An extremely important part of disease prevention is vaccination, which improves the immune response to a particular disease. Vaccines save lives and prevent deadly diseases that used to take millions of lives, especially the lives of infants. They have led to the eradication of smallpox, the near eradication of polio and have prevented billions of deaths worldwide. The idea of vaccination (or variolation) originated in Chinese traditional medicine in which a person was deliberately infected with cowpox. It is consistent with the idea in traditional Chinese medicine that a very low dose of a toxin can help prevent an illness. Since vaccination with weakened smallpox virus is much safer, variolation was banned in England in 1849, but it was used longer in China and it caused an outbreak of smallpox in the 1960s. Edward Jenner first popularized the use of cowpox to immunize humans against smallpox. The word vaccine comes from the Latin word for cow, vacca. In France, Louis Pasteur and others continued the

Robert E. Smith

work. The earliest vaccines were made from partially attenuated virus (smallpox and rabies) or inactivated bacteria (pertussis). Since the 1930s, many vaccines have been prepared by injecting viruses into fertilized chicken eggs. The eggs are kept warm as the viruses multiply for a few days. The eggs are cracked open and the viruses are inactivated using chemicals that chop them into pieces.

In time, more advanced methods were used. This includes chemical treatment of a protein toxin to form a toxoid (such as tetanus, diphtheria), development of a purified and inactivated virus (hepatitis A), development of virus-like particles (such as hepatitis B, human papillomavirus) and the use of purified polysaccharides (pneumococcal vaccines) [1]. "Cell cultures have been used ever since they were first used to develop the polio vaccine. Salk's inactivated polio vaccine was grown in primary monkey kidney cells. There are now Vero cells derived from African green monkey kidneys, Madin–Darby Canine Kidney (MDCK) cells, and PBS-1 cells (HepaLife Technologies, Boston, MA) that are grown either adherently in roller bottles, NUNC cell factories (Thermo Scientific, Roskilde, Denmark), or on microcarriers, or in suspension cultures in stirred-tank bioreactors or disposable wave bioreactors. There are also proprietary human cell lines such as PER.C6® (Johnson & Johnson, Leiden, the Netherlands), AGE1.CR® (ProBiogen, Berlin, Germany), and EB14® (Vivalis, Nantes, France) which are usually grown in suspension cultures in serum-free media. The Vero cell line is currently the most widely accepted by regulatory authorities for vaccine development, and it has been used for over 30 years. The smallpox vaccine ACAM20001 (Sanofi Pasteur, Lyon, France), the pediatric rotavirus vaccines Rotateq1 (Merck, Whitehouse Station, NJ), Rotarix1 (GSK, Brentford, Middlesex, UK), the H5N1 pandemic influenza vaccine Preflucel1 (Baxter, Deerfield, IL) and the Japanese encephalitis vaccine Ixiaro1 (Intercell, Vienna, Austria) are all produced from Vero cell lines grown in containers as large as 7000 L" [1]. By the end of the 20th century, most of the vaccines that could be developed by mimicking natural infection with live attenuated or inactivated viruses or bacteria had been developed [2]. "However, there are still diseases that cause much morbidity and mortality for which there are no immunizations. This includes infections by bacteria in the genuses *Campylobacter and Chlamydia*, the bacteria *Helicobacter pylori* and *Streptococcus* groups A and B. It also includes the

following diseases: dengue fever, leishmaniasis, malaria, schistosomiasis, shigella, tuberculosis and urinary tract infections. It also includes diseases caused by the following viruses: cytomegalovirus, HIV, Epstein-Barr virus (causes mononucleosis), hepatitis C, herpes simplex, and respiratory syncytial virus, rhinovirus. Moreover, a universal flu/influenza vaccine is needed to replace the annual vaccine. Finally, vaccines are being developed to prevent or cure allergies, autoimmune diseases and many forms of cancer" [2].

VIRAL VECTORS

To immunize against diseases caused by viruses, viral vectors are used instead of whole pathogenic viruses [1]. "Adenovirus vectors deliver DNA to target cells, can incorporate cDNA expression cassettes and have a low oncogenic potential because they do not insert their genome into the host DNA. Also, recombinant adenoviruses replicate well in the specific host cell, but do not replicate after being injected into the patient. Viral vaccines can be purified by using polyethyleneglycol (PEG) to precipitate them. Also, conjugated vaccines are made by combining an antigen with a carrier protein that increases the immunogenicity of the antigen. For example, three vaccines against encapsulated bacterial pathogens, *Neisseria meningitides*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b (Hib), were significantly improved by covalently attaching (conjugating) the polysaccharides (PS) in the original vaccines to carrier proteins. The five main carrier proteins used in vaccines today are: tetanus toxoid (TT), diphtheria toxoid (DT), crossreactive material 197 (CRM197), N. meningitides outer membrane protein (OMP), and non-typeable *H. influenza* derived protein D (PD)" [1].

There are also virus-like particles that are used to make vaccines [1]. "They are structural proteins that do not contain a genome and are incapable of a spreading infection. Virus-like particles (VLPs) have a repetitive antigenic structure that is capable of efficiently stimulating both cellular and humoral immune responses. Recombivax HB1 for prevention of hepatitis B infection was the first recombinant protein vaccine for human use. It is made by inserting the gene for a hepatitis B surface antigen (HBsAg) into genetically engineered strains of *S. cerevisiae*. Two VLP-based vaccines for HPV have since been approved by the FDA. They are

CHAPTER 11

Preventing Diseases by Proper Nutrition

Abstract: The five major food groups: cereals, vegetables, fruits, dairy, meat (and meat substitutes), and fats, oils and sweets. A lack of folic acid causes birth defects, such as *spina bifida*, which leaves the victim severely disabled. Folic acid is also found in multi-vitamin supplements, and these are recommended for pregnant women. It is better to eat many types of fish, than to eat red meat. If at all possible, mother's should be encouraged to breast feed their babies. The best-selling, most interesting and controversial dietary supplements are multi-vitamins. The American Medical Association (AMA) does not recommend them. Instead, the AMA recommends getting your vitamins and minerals from a healthy, balanced diet. The National Institutes of Health maintains several pages on their website that have fact sheets on many dietary supplements. The NIH has an office of dietary supplements. It provides information on the use and safety, nutrient requirements, database resources, news and research. However, it is the FDA that has regulatory responsibility for dietary supplements, as dictated by the dietary supplement health and education act, or DSHEA, passed in 1994. The DSHEA indicated that the dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed, but the FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market [1]. The popular dietary supplement, açaí, will make you gain weight – not lose weight. Another supplement, *myo*-inositol, may help prevent lung cancer in smokers.

Keywords: Açaí, AMA, American Medical Association, DSHEA, FDA, Folic acid, Myo-inositol, National Institutes of Health, NIH.

NUTRITION

Modern medicine now recognizes the importance of nutrition in maintaining good health and managing diseases. Although hard science and reductionist thinking were used to determine which nutrients are essential, systems thinking is also needed. The needs of each individual must be considered. For example, in the USA and many countries that emphasize western medicine, over-consumption of calories is a major concern, but in much of the world malnutrition and starvation

Robert E. Smith

are problematic. Malnutrition can be a problem in both cases. The popular fast food diet in the USA may provide plenty of calories, but is often lacking in vitamins and dietary fiber that is found in fruits and vegetables. However, multivitamins seldom do any good to well-fed people and can actually do much harm, especially if they contain iron and are consumed by men over 50. In contrast, vitamins save lives and prevent blindness in many disadvantaged communities.

Water is at least as important as food. Unfortunately, billions of people don't have access to clean water. In parts of the world that have plenty of clean water, many say that it is important to drink at least eight 8-ounce glasses of water every day to maintain good health. Caffeinated beverages, sweetened fruit juices and soft drinks are often considered to be dehydrating, even though usually they are not [1]. The USDA recommends different amounts of water for people of different age and sex, such as 3.7 L/day for adult men and 2.7 L/day for women. Even though sweetened beverages may not be dehydrating, they are a major contributor to obesity in the USA and other countries.

Still, food is essential, and billions of people don't get enough to eat. However, in so-called "developed countries" like the USA, obesity is a major health problem. It can cause diabetes and other diseases. In this chapter, we will learn that proper diet and nutrition can prevent obesity and many diseases. We will learn about the five major food groups: cereals, vegetables, fruits, dairy, meat (and meat substitutes), and fats, oils and sweets. Cereals include bread, oatmeal, rice and pasta. They contain complex carbohydrates. It is better to eat whole grain foods. This includes whole grain bread, as opposed to white bread. It also includes brown and wild rice, as opposed to white rice. Similarly, whole grain pasta is better than white pasta. The USDA recommends eating three or more ounce-equivalents of whole grain products each day [2]. Two cups of fruit and 2.5 cups of vegetables per day are recommended for a 2000 calorie per day diet, suitable for a sedentary man 51 – 70 years old, or a sedentary woman 19 – 30 years old [2]. This does not include the two most popular vegetables in the USA, iceberg lettuce and French fries. It does include all the colorful fruits and vegetables that contain vitamins, minerals and antioxidants.

Antioxidants are nutrients that prevent damage that can be caused by oxidants, that is, reactive oxygen and nitrogen substances, or RONS. The five vegetable subgroups are: dark green, orange, legumes, starchy vegetables and other vegetables. The USDA also recommends consuming 3 cups of fat-free or low-fat milk or equivalent milk products, such as soy milk or other soy products. The USDA recommends 5.5 ounce equivalents from the meat and bean group. This can be lean meat, fish, beans, nuts or seeds. The USDA recommends 24 grams (6 tsp) of oils. There is also a discretionary Calorie allowance of 267 Calories, which can be such things as 18 grams of solid fat (saturated fat, from red meat), or 8 tsp of sugar, in sweetened foods or beverages [2].

Of course, the number of Calories and servings of food should be higher for active people. The estimated daily Caloric intake for active women aged 19 – 30 is 2400 Calories and for active men 19 – 30 years old it is 3000 Calories [2]. Note that there are two different definitions of Calories and calories. In a science class (especially physics), one calorie (lower case) is defined as the amount of energy needed to raise the temperature of one gram of deionized water in the liquid phase by 1^{o}C. Actually, calories and kilocalories are not SI (metric) units and are somewhat imprecise. That is, the exact amount of energy needed to raise the temperature of liquid water by 1^{o}C depends on the starting temperature of the water. Still, the difference in the amount of energy needed to heat liquid water from 1^{o}C to 2^{o}C is very close to the amount of energy needed to heat liquid water from 10^{o}C to 11^{o}C, so the original definition of a calorie is close enough to be used for most practical purposes. One kilocalorie is equal to 1000 calories. One kilocalorie is the amount of energy needed to increase the temperature of 1 kg (1000 g) of water by 1^{o}C. Labels on containers of foods and beverages are based on a different definition. They use the commonly accepted definition that one Calorie (upper case) in food is the same as one kilocalorie as defined by scientists. So, theoretically, the 100 Calories in a small apple have enough stored energy (as carbohydrates) to increase the temperature of 100 kg of liquid water 1^{o}C, if it is burned up completely in a bomb calorimeter.

However, it should be noted that the caloric content of food is not based on an artificial experiment, in which a small sample of food is burned up completely in a bomb calorimeter in the presence of much oxygen. The calorimeter contains a

CHAPTER 12

New Problems and Solutions

Abstract: Many new phenomena emerge at higher levels of organization. For example, it is possible that the virus causes the flu in birds or pigs will mutate to a form that can easily infect and kill people. In addition, as the global climate continues to change, several tropical diseases could appear as cooler regions warm up as the habitats of the carriers of tropical diseases like dengue and yellow fevers spread. It is also possible that the poliovirus or smallpox virus could re-emerge, even though they have been almost eradicated. On the other hand, scientists are creating new, genetically altered life forms, in which some consider an emergent solution, while others consider genetic engineering to be a terrible problem. Scientists use genetic modification (GM), biotechnology, gene splicing and recombinant DNA technology. At the same time, nanotechnology has the potential to turn relatively inactive molecules into potent drugs. Stem cell technology may aslo be able to provide many medical benefits. More recently, there has been a shortage of some important prescription drugs. This can continue to happen if a major producer has problems in manufacturing and has to stop production for a while, or if there is not enough profit to be made and they shut down production. As a result, patients may experience unacceptable delays in receiving 210 different medicines for cancer, anesthesia Parkinson's disease, schizophrenia, osteoporosis and organ failure. Finally, the ebola virus has emerged as a new problem, so therapies and vaccines are being developed.

Keywords: Ebola virus, Emergent properties, Genetic modification, Global warming, Nanotechnology.

EMERGENT PROBLEMS

Many new phenomena emerge at higher levels of organization. Although the word emergent may not be very popular with reductionist thinkers, it has been used by physicians for decades to refer to problems, diseases or epidemics that emerge unexpectedly. We have already discussed two important examples: antibiotic resistant bacteria and multidrug resistant cancers. Another frightening example of a possible emergent problem is the likelihood that the virus that causes the flu in birds or pigs will mutate to a form that can easily infect and kill people. One

Robert E. Smith

doesn't have to go too far back in history to see that a flu virus mutated into a form that caused the deadly influenza pandemic from 1918-1920 [1]. It was caused by an unusually severe and deadly strain of the H1N1 subtype of the influenza A virus [1]. It killed anywhere from 40 – 100 million people, which is more than the number of people killed in World War I or in the pandemic in the Middle Ages that was caused by the Black Death, also known as the bubonic Plague. However, the Black Death killed a larger percentage of people and it changed all of society. Some people died within 24 hours of showing their first symptoms, but others recovered. Entire villages were wiped out, while villages next to them were unaffected. Similarly, some people in affected cities and villages did not get sick and some who got sick did recover. Still, it changed everything. It interrupted the 100 year war between England and France. Peasants started living in abandoned castles. Fields full of crops were left unattended, since nobody was left to harvest them. It is possible that history could repeat itself if new pandemics, such as a contagious bird flu or a virulent form of swine flu, were to emerge. There is already a severe shortage of health care professionals, hospital emergency rooms and mortuaries. If a new pandemic emerges, there won't be anywhere near enough doctors and nurses to care for the patients, and society could become overwhelmed with corpses. It could change everything, just as the Black Death did.

In 2009, the influenza virus in pigs (or swine) began infecting people, but so far it has not been very virulent. Most people infected by it recovered. Still, many people were infected, indicating that the virus had penetrated the human population. Note that the term swine flu was first used, but then it was identified as the H1N1 2009 flu virus. In contrast, the bird flu virus did not pass easily into people, but it was quite virulent in those who became infected, with almost half of them dying.

However, the worst pandemic to emerge in the last part of the 20th century was AIDS. It has killed about 25 million people since it was first recognized in 1981, and about 33 million people are affected by HIV worldwide [2]. It can be especially bad in poorer countries and people who can't afford to buy drugs to treat AIDS that have been patented by major pharmaceutical companies. In the absence of antiretroviral therapy, the average time from HIV infection to AIDS

was nine to ten years [2] but can be much longer with HAART therapy. The average survival time after developing AIDS is about 9.2 months, but can range from two weeks to 20 or more years [2]. With recent developments in antiretroviral therapy, it is hoped that people can live even longer with HIV and research continues to develop better drugs and possible vaccines. Moreover, people who are homozygous (have two copies) of an altered version of the CCR5 white blood cell receptor are resistant to some strains of HIV [2]. Still, HIV is capable of mutating into forms that are resistant to antiretroviral therapy, so extensive research continues. Also, some countries (Brazil and India) are by-passing patent laws, so that they can obtain much cheaper generic versions of AIDS drugs and save millions of lives.

Other diseases have the potential to emerge and cause an enormous loss of life and human suffering. The strain of bird flu, called Influenza A virus subtype H5N1 [3] is endemic in many types of birds, especially in Southeast Asia. It has directly killed tens of millions of birds and caused the culling of hundreds of millions of other birds, in an attempt to keep it from spreading [3]. Some people have caught this form of influenza by being in contact with affected birds, especially chickens. About 60% of those infected have died. So far, there is no evidence that H5N1 can be transmitted from one person to another. However, if H5N1 ever mutates into a strain that can be transmitted between people, it could kill up to 150 million people [3]. Billions of dollars are being spent to develop influenza vaccines that might be able to prevent a pandemic [3]. Also, a strain of H5N1 that can be transmitted to ferrets was genetically engineered [4]. It can be used to study human adaptation to the virus [4].

GLOBAL CLIMATE CHANGE

Other diseases could emerge, too. As global warming continues, several tropical diseases could appear in cooler regions [5]. “Disease-carrying mosquitoes are spreading as climate shifts allow them to survive in formerly inhospitable areas” [5]. “The year 2012 was the worst year ever in Texas for illness caused by the West Nile virus. Mosquitoes that can carry dengue fever viruses were previously limited to elevations of 3,300 feet but recently appeared at 7,200 feet in the Andes Mountains of Colombia. Malaria has been detected in new higher-elevation areas

CHAPTER 13

Communication and Signaling in Medicinal Chemistry

Abstract: To sustain life and good health, it is essential that cells and tissues can communicate with each other. Organelles within cells, cells within tissues, tissues within our body, and all of the bodies in a society must sense their internal and external environments and respond appropriately to changes. Hormones, neurotransmitters and cytokines can act as primary messengers. Secondary messengers include is Ca^{2+}, IP_3 and diacyl glycerol (produced by the hydrolysis of phosphoinositides), arachidonic acid (produced by the hydrolysis of phospholipids that have arachidonoyl on carbon number 2 of the glycerol backbone), ceramide, eicosanoids, lysophosphatidic acid, NO (nitric oxide), cAMP and cGMP. The IP_3 receptor, or IP_3R is a membrane-bound complex of glycoproteins. It is a Ca^{2+} channel that is activated by IP_3, which is a secondary intracellular messenger. Inter- and intracellular communication can be thought of as a network that contains many items (nodes) that have anywhere from one to thousands of connections. The most widely connected nodes are called hubs. Probably the major genetic hub in human and many other mammalian cells is the gene TP53 which codes for the protein p53. About 50% of all human cancers have one or more mutations in p53 that alter DNA transcription.

Keywords: Arachidonic acid, Calcium, Ca^{2+}, Ceramide, cAMP, cGMP, Diacyl glycerol, Eicosanoids, GPCR, IP_3, Lysophosphatidic acid, Nitric oxide.

INTRODUCTION

To sustain life and good health, it is essential that cells and tissues can communicate with each other. Biochemical messengers are made inside subcellular organelles, at the cell membrane and by symbiotic bacteria. These biochemicals can affect nearby cells in paracrine signaling or distant cells in the endocrine system. It is important that the whole process is properly controlled. This is donr through networks, which contain nodes (such as organs, tissues, cells, membranes, organelles, and biochemicals) that are linked to each other. Information flows between nodes, so that the network can adapt to changes in the

Robert E. Smith

external and internal environments and make appropriate changes in those environments. Information about the internal and external environments is continuously being sent and analyzed the messengers. Primary messengers, such as hormones and neurotransmitters bind to receptors, which can amplify the signal through secondary messengers that cause cellular and physiological responses. The primary signal is transduced, or changed, into a secondary signal, such as intracellular Ca^{2+}. To ensure ruggedness and complete transfer of information, there is much cross-talk and redundancy between different pathways. This produces a robust system that enables us to adapt to environmental changes, so homeostasis can be maintained. The whole body is involved in this carefully controlled system.

The conscious mind often leads one to assume that the brain controls everything. This is wrong. Our brains work in concert with the rest of our body to influence our activities. That is, the wholeness of life is an important concept in medical science. We might artificially divide the body into different components to study them, but everything is linked to everything else [1, 2]. For example, some receptors are found in the brain, but other forms of the same receptors exist in other parts of the body. For example, acetylcholine receptors are located throughout the body and brain. Other neurotransmitters, including glutamate, serotonin and norepinephrine, are found in other parts of the body. This is one reason why drugs that affect neurotransmitter uptake in the brain can have side effects in other parts of the body.

So, there are molecules called neurotransmitters that are one type of primary messenger. They send information from the one neuron to another at synapses, or from neurons to muscles at neuromuscular junctions. However, some of these neurotransmitters are also found in other parts of the body, such as the stomach and the tongue. The stomach can send signals to the brain to indicate hunger or satiety. Similarly, tongues have taste buds that tell our brains if the things we put in our mouths taste good. For example, the excitatory neurotransmitter glutamic acid can bind to glutamate receptors on our tongues, which adds flavor to foods that contain it. That is why Chinese food often contains the sodium salt of glutamate (monosodium glutamate, or MSG). This is just one example of how a primary messenger can start the flow of information.

So, let us look closer at the biology of information flow, signaling and receptors. Organelles within cells, cells within tissues, tissues within our body, and all of the bodies in a society must sense their internal and external environments and respond appropriately to changes, for the good of the cells, tissues, whole person and society. This includes the approximately 10^{11} neurons in the brain [3]. They are interconnected in a network that send and receive information within the brain and respond to information coming from the rest of the body. Moreover, we receive much information from the external environment and from people around us in a society. We compare this to information we have learned throughout our lives and try to make appropriate responses. At the same time, the immune network responds to stress caused by the brain's reaction to stimuli. For example, depression can be bad for the immune system. In any case, information is sent in the form of messengers. Hormones, neurotransmitters and cytokines can act as primary messengers. Most of these bind to protein receptors on the outside of a cell, but some hormones bind to intracellular receptors.

Some of these receptors amplify the primary message by making many secondary messengers, which cause important effects inside the cell. The most widely used second messenger is Ca^{2+}, which is stored in the endoplasmic reticulum (ER). Once released from the ER, Ca^{2+} can bind to some cytosolic molecular messengers directly, but can only bind to others indirectly. Instaed, it can bind to the protein calmodulin, which can then bind to and affect other protein messengers, such as the calcium/calmodulin (CaM)-dependent protein serine-threonine kinases (CaMKs). In excitable cells (such as neurons), Ca^{2+} can also enter the cell from outside of the cell by passing through voltage and ligand-gated Ca^{2+} channels on the cell membrane. In muscle cells, the hormone adiponectin causes extracellular Ca^{2+} to enter the cell, activating the adiponectin receptor 1, which activates protein kinases and changes mitochondrial activity. Decreased levels of adiponectin and its receptor help cause the mitochondrial dysfunction and insulin resistance that occurs in diabetes.

In addition, Ca^{2+} and calmodulin dependent protein kinase II (CaMKII) have important regulatory functions in the heart and brain, and when chronically activated, it can be pathological [4]. "For example, acute hyperglycemia can lead to the attachment of N-acetylglucosamine to CaMKII, which activates it. Under

CHAPTER 14

Systems Thinking in Medicinal Chemistry

Abstract: Systems biology is essential for P4 medicine, as are autopoiesis, network theory and the concept of emergent properties. That is, the basic, fundamental unit of life is the cell, not the atoms and molecules in the cell. Many new properties emerge when atoms, molecules and ions are organized in a living cell. The functions of a cell do not depend on just the properties of the individual molecules, but also on how these molecules interact. Autopoiesis means self-production. It is a network of production processes, in which the function of each component is to participate in the production or transformation of itself and the other components in the network. The production processes are circular. Life is a cyclic process that produces the components of a living system. Based on the autopoietic theory of life, the biosphere of Earth is often thought of as a living system. Bacteria can be thought of as the catalysts that maintain the atmosphere in its present state, far from equilibrium, but stable, like homeostasis in a cell, organ or organism. Networks permeate living systems. Living systems and the internet are examples of a type of network called a scale-free network. These networks are dominated by a few well-connected nodes, called hubs. Most nodes in the network have a few connections, but a small number of nodes have a seemingly unlimited number of connections. In the scale-free network that is in living cells, there are many levels of organization. Each of them can be viewed as a network. There is a network of genes, a metabolic network, a regulatory network and a cellular network.

Keywords: Autopoiesis, Gaia, Hubs, Nodes, Scale-free network, Systems biology.

SYSTEMS BIOLOGY

Systems biology has always been behind traditional medicine and is now an integral part of modern, westernized medicine. It is essential for P4 medicine, as are autopoiesis, network theory and the concept of emergent properties. That is, the basic, fundamental unit of life is the cell, not the atoms and molecules in the cell. This is because many new properties emerge when atoms, molecules and ions are organized in a living cell. Moreover, almost all of the atoms, molecules and ions in our cells are continuously being broken down or replaced. This

Robert E. Smith

happens while the organization and appearance of adult organisms remains nearly constant. There are slow, gradual changes as we age and much faster changes as a fetus develops, a baby is born and an infant grows. Important changes also occur during pubescence and again during and after menopause. Still, the changes are much slower than those that occur in the atoms, molecules and ions. For example, the skin cells and molecules in them are replaced every few days. So, the hands that we shake when we first meet someone look the same way when we see them a few days later, as does our face. We may feel and look the same while the organization of our cells and tissues remains nearly constant, but the molecules are different. So, one's anatomy, physiology and even personal identity don't change either. They are based on the same cells and tissues, even though the molecules have changed. We can't be reduced to a collection of fundamental subatomic or atomic particles, as suggested by reductionist thinking.

However, math - the foundation of reductionist thinking - is still essential. In reductionist thinking, quantitative mathematics is the basis for all science. Many consider it to be the only true science, since it can produce linear equations that can calculate exact answers to questions that are asked properly. That is, if a mathematician, physicist or chemist knows the position and momentum of a piece of matter, as well as all the forces acting on it, its position and momentum at any time in the future can be calculated with no uncertainty. Unfortunately, it is almost never possible to know all the forces that are acting on a piece of matter. Still, for practical purposes, many of the forces can be ignored. For example, friction can be ignored when calculating the position and momentum of a 10 kg rock that is falling off a cliff. They can be calculated by simple linear equations, such as force equals mass times acceleration. It is even possible to calculate the position and momentum of two large objects that revolve around each other (such as two stars in a binary system that has no planets).

However, there are no exact solutions to the non-linear equations that are needed to calculate the position and momentum of three objects, such as the sun, Earth and moon. Still, they can be calculated well enough to enable us to put men on the moon and send the SOSO Solar and Heliospheric Observatory to orbit the sun and study it. However, many aspects of life can only be described by non-linear equations that have no exact solution, but many approximate solutions. This can

be especially important to Gaia and the survival of humanity. That is, there are many different ways that Gaia can change in response to variations in her temperature. For example, to redistribute the solar energy that reaches the tropics, ocean currents such as the Gulf Stream emerged that carry warm water to Western Europe, giving it a temperate climate, as opposed to the much colder climate in similar latitutes in Canada and Russia. This, like other ocean currents, is driven by differences in NaCl concentrations (salinity) between surface and underlying ocean water. That is, as salty ocean water freezes at in Polar regions, the ice that is produced has very little dissolved NaCl, but the liquid water that remains on the surface becomes enriched in NaCl. As more and more polar ice melts, the salinity of the water will decrease. This will decrease the force that drives the thermohaline overturning current and may eventually change or even stop the Gulf Stream. This could make the climate of England feel like that in Siberia. Similarly, an anomalous high pressure atmospheric system caused record high temperatures in the Alaska and the Western USA, while forcing cold, Polar air into the Noertheast. This caused record cold and snowfalls. So, the current set of approximate solutions to the non-linear equations that drive weather and climate can change to different solutions that may have devastating effects.

Similarly, human biology is based much more on non-linear than linear equations. There is even much debate on whether life can be completely described by mathematics, or even by physics or chemistry. For example, the autopoietic theory of life holds that cognition and self-awareness are emergent properties of life. So a corollary to this is that non-living computers and robots can never become self aware or have feelings. Others feel that it is possible that consciousness can be described by math and that computers may eventually become self aware. So far, there is probably insufficient data to know one way or the other.

This should not be confused with the Heisenberg uncertainty principle that states that both the exact position and momentum of a single electron can never be known simultaneously. It is the very nature of the electron. So, we may not be able to calculate the position and momentum of every single electron in a glass of water, we can be sure that we can drink it and satisfy our thirst. On the other hand, there are many aspects of life that can’t be described by quantitative mathematics. That is, graph theory and network theory have emerged as crucial tools in learning

Appendix

Structures of Small Molecule Drugs and Hormones Discussed in This Edition

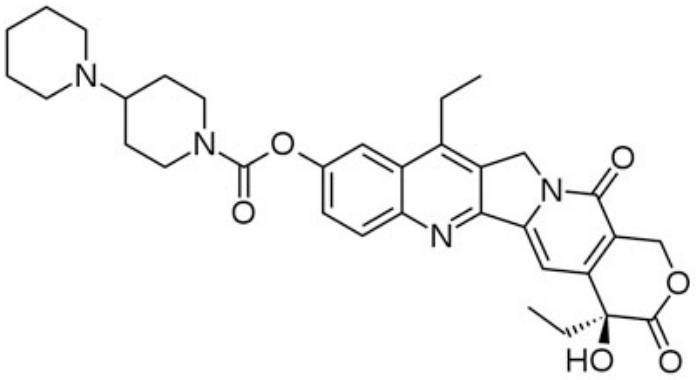

Fig. (1). Camptosar.

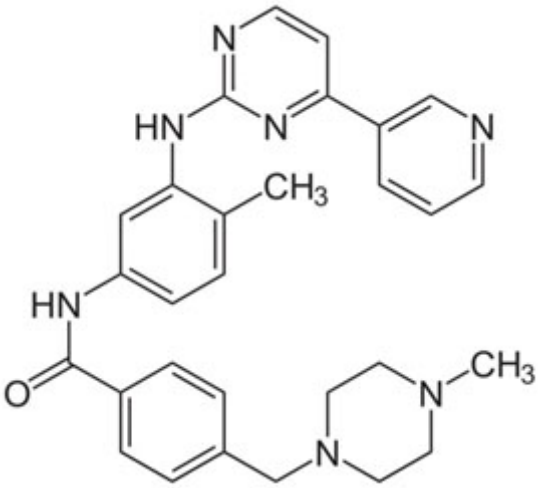

Fig. (2). Imatinib, Gleevec® for chronic myeloid leukemia.

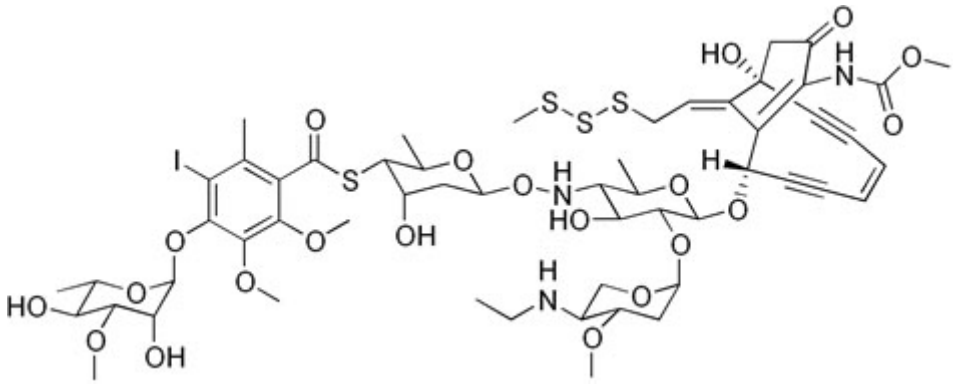

Fig. (3). Calicheamicin.

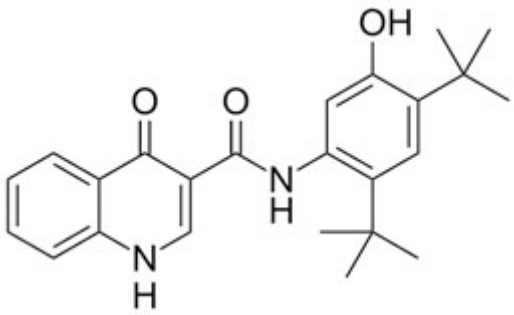

Fig. (4). Ifacaftor, Kalydeco®, for cystic fibrosis.

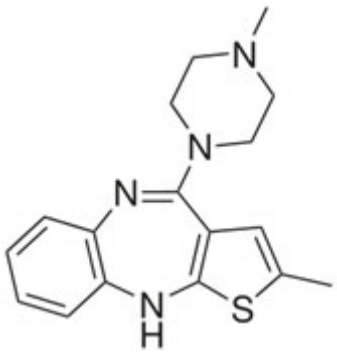

Fig. (5). Olanzapine Zyprexa®, an atypical antipsychotic.

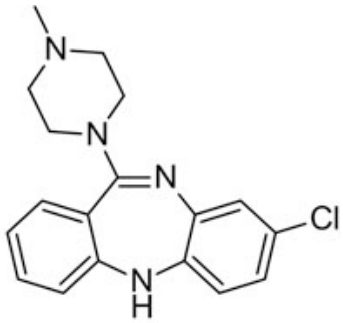

Fig. (6). Clozapine, an atypical antipsychotic.

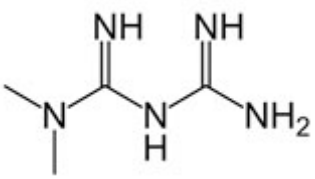

Fig. (7). Metformin (Glucophage®).

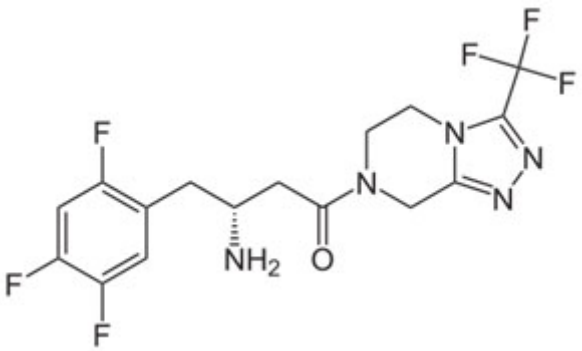

Fig. (8). Sitagliptin, Januva®, an antidiabetic that inhibits dipeptidyl peptidase-4 (DPP-4).

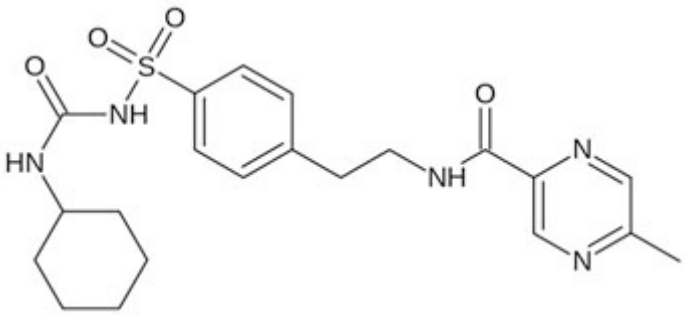

Fig. (9). Glipizide, (Glucotrol®), CYP substrate and oral antidiabetic.

SUBJECT INDEX

A

Adaptive 9, 78, 82, 108, 121, 147, 148, 221, 330, 331, 338, 360, 370, 376, 383, 386, 430
Alzheimer's disease 35, 288
AMA 435, 458, 483, 484
American Medical Association 435, 458, 462, 483, 484
Arachidonic acid 74, 76, 282, 294, 351, 538, 541
Arthritis 69, 72, 83, 97, 130, 134, 290, 355, 367, 373, 380, 439, 445, 459, 514, 533, 645
Autoimmune diseases ii, 10, 78, 235, 290, 300, 323, 325, 342, 344, 350, 352, 354, 362, 377, 378, 387, 414, 544
Autonomic nervous system 198, 199, 209, 226, 256, 264, 265, 268, 275, 311, 313
Autopoiesis ii, 219, 257, 327, 505, 552, 559, 566, 570, 571, 573, 575, 589, 591
Avastin 3, 39, 145, 188, 362

B

Bacteria 39, 48, 70, 75, 83, 151, 235, 253, 260, 278, 338, 340, 348, 364, 377, 378, 380, 386, 393, 395, 413, 415, 417, 419, 429, 440, 457, 478, 483, 494, 497, 499, 500, 515, 538, 552, 561, 570, 587-589
Biomarkers 3, 4, 7, 9, 13, 14, 17, 29, 49, 57, 67, 82, 138, 150, 161, 174, 194, 218, 253, 371, 504, 509, 532

C

Calcium 75, 126, 127, 131, 187, 198, 203, 222, 223, 227, 318, 453, 455, 460, 468, 483, 488, 512, 538, 540, 604
cAMP 191, 203, 205, 208, 228, 538, 545, 546, 548
Campath 3, 39
Cancer i, ii, 3, 5, 7, 25, 26, 45, 46, 48, 49, 51, 54, 72, 78, 97, 114, 131, 135, 211, 212, 216, 225, 236, 237, 240, 243, 245, 248, 253, 254, 280, 281, 283, 287, 301, 317, 326, 327, 335, 344, 346, 350, 352, 365, 366, 372, 373, 377, 379, 381, 384, 385, 398, 405, 408, 422, 434, 435, 439, 442, 465, 471, 473, 475, 478, 482, 484, 500, 530, 532, 535, 537, 562, 569, 591, 617, 644, 647, 661, 662
Ceramide 538, 541
cGMP 217, 229, 278, 314, 508, 528, 538, 541, 545, 546
Chicken pox 412, 417, 431

D

Diabetes 33, 35, 53, 67, 69, 72, 76, 83, 86, 88, 92, 93, 96, 98, 100, 101, 113, 114, 116, 118, 119, 130, 131, 203, 205, 216, 225, 230, 235, 253, 294, 366, 370, 436, 445, 446, 473, 507, 511, 514, 520, 522, 533, 536, 540, 544, 599, 654, 655
Diacyl glycerol 102, 133, 160, 538, 541
Diphtheria 425, 426, 431, 432
DSHEA 435, 469, 470, 478, 479, 484

E

Ebola virus 35, 494, 529, 536, 537
Eicosanoids 71, 74, 75, 112, 116, 538, 541
Emergent properties 494, 552, 554, 556-559
Erbitux 3, 39, 145, 188, 356, 362

F

FDA ii, 3, 5, 6, 8, 9, 27, 28, 42, 43, 51, 52, 58, 61, 62, 97, 98, 103, 118, 119, 129, 132, 145, 149, 162, 163, 167, 168, 173, 186, 187, 190, 196, 203, 239, 243, 246, 248, 252, 253, 281, 285, 286, 295, 298, 303, 304, 312, 314, 320, 321, 332, 337, 339, 357, 360, 362, 367, 372, 377, 384, 386, 389, 401, 402, 405, 409, 414, 415, 421, 425, 427, 432, 433, 435, 443, 456, 473, 475, 478, 479, 484, 492, 508, 509, 513, 526, 528, 534, 537, 653
Flu virus 370, 397, 412, 423, 424, 431, 495
Folic acid 292, 293, 435, 456, 457, 459, 460, 482
Fungi 323, 325, 326, 332, 395, 399, 405, 408, 409, 426, 570, 576

G

Gaia 552, 554, 570, 574, 575, 589, 592
Gemeprost 226, 234, 241, 249, 251, 626
Gene chips 3
Genetic modification 451, 494, 497, 527, 528
Global warming 370, 441, 450, 494, 496, 497, 501, 526, 530
GPCR 77, 84, 97, 132, 186, 202, 208, 228, 237, 252, 302, 388, 538, 543, 550

H

HAART 323, 374, 375, 381, 382, 387, 496
Heart disease ii, 11, 17, 69, 72, 73, 76, 78, 80, 83, 86, 88, 92, 94, 96, 103, 120, 122, 125, 130, 131, 172, 244, 287, 335, 428, 439, 444, 447, 459, 466, 467, 473, 474, 482, 489
Hepatitis A 412, 413, 417, 418, 425, 431, 432
Hepatitis B 81, 138, 151, 188, 375, 382, 406, 431, 432
Herceptin 3, 5, 37, 39, 145, 161, 162, 183, 188
HIV 12, 16, 58, 184, 323, 336, 338, 358, 359, 386, 387, 392, 393, 398, 414, 415, 418, 426, 428, 429, 431, 495, 496, 503, 511, 516, 530, 534
HPV 42, 60, 184, 339, 412, 414, 415, 417, 418, 422, 426, 427, 431, 434
Hubs 538, 552, 576, 577, 579, 580, 582, 583, 587, 590
Human papilloma virus 42, 60, 138, 151, 188, 339, 412, 415, 418, 426, 431

I

Immune system i, 42, 70, 71, 75, 78, 79, 82, 93, 103, 108, 111, 116, 121, 139, 147, 148, 152, 167, 205, 218, 219, 234, 235, 238, 257, 266, 271, 273, 274, 290, 292, 300, 310, 339, 342, 349, 370, 371, 373, 374, 377, 380, 386, 396, 406, 417, 426, 430, 457, 458, 460, 461, 489, 540, 558, 617
Infectious diseases i, ii, 341, 389, 395, 396, 399, 408, 410, 587
Inflammation i, ii, 48, 92, 96, 98, 102, 112, 113, 119, 129, 148, 216, 275, 289, 294, 300, 324, 325, 361, 371, 378, 390, 394, 416, 426, 439, 444, 452, 459, 471, 476, 513
Innate 75, 77, 79, 81, 82, 84, 86, 87, 108, 147, 221, 235, 330, 331, 338, 340, 342, 354, 357, 358, 360, 364, 365, 370, 386, 389, 396, 430, 558
IP3 133

L

Levonorgestrel 226, 234, 249, 251, 623
Lysophosphatidic acid 538, 541

M

Measles 58, 398, 412, 417, 418, 424, 431, 432, 434