

Contents

Preface

page vii

PART ONE: TOPICS OF GENERAL INTEREST

1. Toxicity in the Service of Man	3
1.0 What is 'selective toxicity'?	3
1.1 The scientific basis of selectivity	8
1.2 Selectivity through differences in distribution	11
1.3 Comparative cytology as a basis for selectivity	13
(a) <i>The cell wall</i> (b) <i>The cytoplasmic membrane</i> (c) <i>The endoplasmic reticulum and 'smooth microsomes'</i> (d) <i>Mitochondria and Chloroplasts</i> (e) <i>Ribosomes, and some other organelles</i> (f) <i>The nucleus</i> (g) <i>Viruses</i>	
1.4 Comparative biochemistry as a basis for selectivity	30
(a) <i>Nucleic acids</i> (b) <i>Proteins</i> (c) <i>Nitrogen and phosphorus metabolism</i> (d) <i>Carbohydrate and lipid metabolism</i> (e) <i>The tricarboxylic acid cycle, and electron transport</i> (f) <i>Photosynthesis</i> (g) <i>Enzymes, coenzymes, and hormones</i> (h) <i>Metabolism of foreign substances</i> (i) <i>Quantitative aspects</i>	
1.5 Conclusion	65
2. Absorption, Distribution, and Excretion	66
2.0 Introduction	66
2.1 The concept of 'Receptors'	68
2.2 The permeability of natural membranes	71
2.3 'Sites of Loss', and synergism	82
2.4 Degradation before action	91
2.5 Reversibility of combinations with receptors	98
2.6 Quantitative aspects of distribution	100
3. Chemotherapy: History and Principles	103
3.0 Introduction and early history	103
3.1 Ehrlich's fundamental contributions	104
3.2 Chemotherapeutic drugs available before 1935	109
3.3 1935 and afterwards	114
3.4 Parallel developments in insecticides and crop-protecting agents	123
3.5 Resistance to drugs and other agents	129
3.6 Therapeutic interference	138

4. Pharmacodynamics	I42
4.0 Introduction. Pharmacodynamics and chemotherapy compared	I42
4.1 Early history of the search for new drugs by synthesis	I43
4.2 The value of measurement	I45
4.3 Hypotheses of the mode of action of drugs	I46
4.4 Some common molecular patterns in drugs with pharmacodynamic action	I59
4.5 Simplification of the structure of natural products	I62
4.6 The natural divisions of pharmacodynamics	I69
(a) <i>Drugs acting on the central nervous system</i>	
(b) <i>Drugs acting on peripheral nerve-fibres</i>	
(c) <i>Drugs acting at peripheral nerve-endings</i>	
(d) <i>Drugs acting on other tissues</i>	

PART TWO: THE RELATIONSHIP BETWEEN STRUCTURE AND BIOLOGICAL ACTIVITY

5. The Chemical Basis of Selectivity. The nature of Bonds.	
Adsorption	I81
5.0 Introduction	I81
5.1 Types of chemical bond	I82
5.2 Adsorption	I88
5.3 Some non-biological examples of chemical specificity	I91
5.4 Experiments illustrating selective adsorption	I93
6. Metabolites, Enzymes, and Metabolite Analogues	I95
6.0 Introduction	I95
6.1 Metabolite analogues: definition, preparation, and mode of action	I99
6.2 History of metabolite antagonism prior to 1940	206
6.3 The sulphonamides and other folic acid antagonists	208
(a) <i>How sulphonamide drugs antagonize synthesis of folic acid</i>	
(b) <i>The role of folic acid derivatives in nature</i>	
(c) <i>Agents that antagonize reactions of the pteridine nucleus</i>	
6.4 Other metabolite analogues of proven value in selective toxicity	220
6.5 Sequential blocking	227
6.6 Analogues which form a covalent bond	229
6.7 Metabolite antagonists that are not analogues	230
6.8 Pharmacogenetics	231
7. The Influence of Methyl-groups on Biological Action	232
7.0 Introduction	232

7.1 Steric influences	232
(a) <i>On solubility</i> (b) <i>On covalent hydration</i> (c) <i>On chelation</i> (d) <i>On receptors and enzymes</i>	
7.2 Electronic influences	239
(a) <i>On ionization, and reduction</i> (b) <i>On carcinogenic hydrocarbons</i> (c) <i>On covalent reactivity</i>	
8. Ionization	245
8.0 Introduction	245
8.1 The nature of ionization	245
8.2 Differences in ionization which can assist selectivity	254
8.3 Substances that are more biologically active when ionized	260
(a) <i>The antibacterial aminoacridines</i> (b) <i>Cationic antibacterials which have the aminoacridine type of action</i> (c) <i>Cationic and anionic antibacterials with other types of action</i> (d) <i>Antiprotozoal examples</i> (e) <i>Antiviral examples</i> (f) <i>Pharmacodynamic examples</i>	
8.4 Substances that appear to be less active when ionized	283
8.5 Substances of which both ion and molecule play a part in the biological action	287
8.6 The ionization of receptors	293
8.7 Conclusions	295
9. Metal-binding Substances	297
9.0 Introduction	297
9.1 Metals in the living cell	298
9.2 Biochemical differences which can assist selectivity	305
9.3 The chemistry of chelation	310
9.4 Chemical differences which can assist selectivity	320
9.5 The various modes of biological action of chelating agents (an introduction)	326
9.6 Diminution of the toxic effect of a metal by chelation	329
9.7 Augmentation of the toxic effect of a metal by chelation	331
(a) <i>Mode of action of 8-hydroxyquinoline (oxine)</i> (b) <i>Substances chemically related to oxine</i> (c) <i>Substances not chemically related to oxine, but acting similarly</i>	
9.8 Chelating substances whose biological action may not be due entirely to chelation	343
9.9 Fundamental considerations in designing new chelating agents. . . Promising avenues of application	350
10. The Covalent Bond in Selective Toxicity	353
10.0 Introduction	353
10.1 Arsenicals, antimonials, and mercurials	353

10.2	Penicillin, and similarly acting substances	359
10.3	Organic phosphates and carbamates	366
10.4	Alkylating agents	373
10.5	Lethal synthesis and lethal incorporation	378
10.6	Miscellaneous examples	382
11.	Steric Factors	384
11.0	Introduction	384
11.1	Optical isomerism	387
11.2	Geometrical isomerism	391
11.3	Conformational behaviour	393
11.4	Drugs and their receptors	395
	(a) <i>Catecholamine receptors</i> (b) <i>Acetylcholinesterase</i> (c) <i>Acetylcholine receptors</i> (d) <i>Morphine and other analgesics</i>	
11.5	Conclusion	418
12.	Surface Chemistry. The modification of Membranes by Agents	419
12.0	Introduction	419
12.1	Surface phenomena and biological activity	421
12.2	The injury of membranes by biologically active agents	424
13.	Free Radicals	430
13.0	Introduction	430
13.1	The occurrence of free radicals in the use of selectively toxic agents	431
14.	Biological Activity unrelated to Structure. Ferguson's Principle	436
14.0	Introduction	436
14.1	Biological depressants (hypnotics, general anaesthetics, and volatile insecticides)	436
14.2	Mitotic disorganizers	448
14.3	Sorptive dusts	449
	Appendices	
I	Connexion between ionization and antibacterial activity in the acridine series	452
II	Calculation of percentage ionized, given pK_a and pH	458
III	Some physical effects of substituents	460
	Bibliography	464
	Subject Index	507