•

PREFACE	xvii
SUMMARY	1
CHAPTER 1. Heterosis, Polymorphism and Selection	
I. Heterosis and 'hybrid vigour'	9
II. Problems in the study of heterosis	11
A. The problem of analysing measurements	11
B. The problem arising from different theoretical explanations for	-
heterosis	13
(a) The dominance theory	13
(b) Inbreeding depression as the opposite of (positive) heterosis	13
(c) Overdominance	14
(d) Epistasis	14
(e) Complementation	14
C. The problem of considering genetic loci as independent entities—the	
paradox of segregational genetic load	15
D. Stratification of a population generating a deficit of heterozygotes	17
without negative heterosis	17
E. Stratification of a population generating an excess of heterozygotes without positive heterosis	10
F. The problem of differences in 'genetic background'	18 19
G. The problem of 'gene-environment interaction'	19
III. How strong must selection or stratification be in order to be detected?	20
IV. More sophisticated approaches to the study of selective advantage of	20
polymorphisms in populations	22
V. Positive heterosis vs. frequency dependent and cyclical selection	25
A. Differences in opinion on positive heterosis	25
B. Frequency dependent selection	26
1. Mimicry	26
2. Disruptive selection	26
3. Polymorphism and disease resistance	28
4. Molecular mimicry	31
5. Frequency dependent selection and positive heterosis at the	
Esterase-6 locus in Drosophila melanogaster	31
C. Cyclical selection	32
Cruser a c	
CHAPTER 2. Some Aspects of Molecular Biology Relevant to Protein Poly- morphism and Heterosis	
I. Levels of protein structure	34
A. Primary, secondary and tertiary structure	34

B. Quaternary structure	36
1. Subunits and hybrid molecules	36
2. Biquaternary proteins	37
(a) Haemoglobin (abbreviated Hb)	37
(b) Lactate dehydrogenase (abbreviated LDH)	37
3. Configuration	38
C. Quintary structure (macromolecular ensembles)	40
II. Gene mutation and gene duplication	41
A. Single amino acid substitution mutations	41
B. Rarer types of gene mutation	44
1. Intracistronic duplication	44
2. Fusion mutations—the haemoglobin Lepore's	46
3. Clean deletions	46
4. Dirty deletions-frame-shift mutations	47
C. Gene duplication	48
D. Gene deletion and null alleles	50
CHAPTER 3. Protein Heterogeneity	
I. Starch gel electrophoresis and the study of protein heterogeneity	54
II. Chemical classification of protein heterogeneity	54
A. Gene duplication, followed by mutational divergence	55
B. Ambiguity in the translation of certain codons	55
C. Protein polymorphism <i>sensu stricto</i> (allelic variation)	56
D. Configurational isomers	56
E. Dissociation and aggregation	57
F. Combination with large molecules which are distinct entities	57
G. Combination with small molecules or ions	58
H. Biosynthetic chemical modification	60
I. Proteolytic modification	61
J. Modification of -SH and -S-S- groups	62
K. Amidation and deamidation	63
III. Biological classification of protein heterogeneity	63
A. Protein polymorphism <i>sensu stricto</i> (allelic variation)	63
B. Cellular specificity	65
C. Subcellular specificity	66
D. Sexual specificity	67
E. Temporal specificity	68
1. Temporal specificity of lactate dehydrogenase	68
2. Temporal specificity of haemoglobin	69
F. Polymorphism of control genes?	72
1. The thalassaemias	72
2. The 'high Hb F' conditions	74
3. Modification of the human haemoglobin temporal specificity	
associated with abnormalities in chromosome number	75
4. Haemoglobin C in sheep-interaction of polymorphism at a	
structural gene and adaptational specificity	76
CHAPTER 4. Patterns of Protein Polymorphism. I. Major Proteins of Body Fluids and Tissues—No Hybrid Zones for Heterozygotes	
	00
I. Classification of proteins and their allelic variation	80
II. Haemoglobin (and myoglobin)	83

III. Serum proteins A. Prealbumins

viii

93 94

2	0	N	T	E	NT	T	C
U	U	IN	1	E	IN	T	0

ix

B. Serum albumin	95
C. Postalbumin	97
D. Gc globulin	97
E. Caeruloplasmin	97
F. Haemopexin (serum haem-binding protein)	98
G. Haptoglobin	99
H. Transferrin	100
	103
IV. Milk proteins	104
A. a-Lactalbumin	104
B. β-Lactoglobulin	104
C. The caseins	
D. Lactoferrin	105
V. Egg white proteins	106
A. Ovalbumin	107
B. Miscellaneous egg white proteins	108
C. Conalbumin (ovotransferrin)	109
VI. Miscellaneous major proteins of tissues	112
A. Low ionic strength extractable proteins of whole Drosophila	114
B 'Myogen' fraction from fish muscle	114

CHAPTER 5.	Patterns	of	Protein	Polymorphism.	II.	Enzymes-No	Hybrid
	Zones for	r He	eterozygo	otes			

I. Oxidoreductases	115
A. Lactate dehydrogenase (EC No. 1.1.1.27) of the hagfish	115
B. Glucose-6-phosphate dehydrogenase (EC No. 1.1.1.49)	115
C. L-amino acid oxidase (EC No. 1.4.3.2)	120
D. Peroxidase (EC No. 1.11.1.7)	121
II. Transferases	121
A. Adenylate kinase (EC No. 2.7.4.3.)	121
B. Phosphoglucomutase (EC No. 2.7.5.1)	122
III. Hydrolases	123
A. Esterases (EC No. 3.1)	123
B. Phosphatases (EC No. 3.1.3)	127
C. a-Amylases (EC No. 3.2.1.1)	130
D. Lysozyme (EC No. 3.2.1.17)	131
E. Peptidases (EC No. 3.4)	132
F. Adenosine deaminase (EC No. 3.5.4.4)	135
IV. Lyases	136
A. Carbonic anhydrase (EC No. 4.2.1.1)	136

CHAPTER 6. Patterns of Protein Polymorphism. III. Enzymes and Other Proteins—with Hybrid Zones for Heterozygotes I. Quaternary structures and hybrid zones—single heterozygotes and

1	Quaternary structures and hybrid zones—single heterozygotes and	
	double heterozygotes for biquaternary proteins	138
Ι	I. Major proteins of body fluids and organ extracts	143
	A. Some polymorphisms and hybrids of haemoglobin from teleost fishes	143
	B. Haemerythrin variants in sigunculids	143
	C. Human haptoglobin	146
	D. Slow a_2 serum globulin (a_2 macroglobulin)	146
	E. Pupal protein from the haemolymph of the flour moth <i>Ephestia</i>	
	Kunniella	147
	F. Major liver protein of bats	148

III. Oxidoreductases	148
A. Alcohol dehydrogenase (EC No. 1.1.1.1)	149
B. 'Nothing dehydrogenase' (but not alcohol dehydrogenase) (EC No.	
1.1.1.?)	153
C. a-Glycerolphosphate dehydrogenase (EC No. 1.1.1.8)	154
D. L-lactate dehydrogenase (EC No. 1.1.1.27)	154
E. NAD-dependent L-malate dehydrogenase (EC No. 1.1.1.37)	158
F. NADP-dependent L-malate dehydrogenase ('malic enzyme') (EC	
No. 1.1.1.40)	161
G. NADP-dependent L_s -isocitrate dehydrogenase (EC No. 1.1.1.42)	162
H. 6-Phosphogluconate dehydrogenase (EC No. 1.1.1.44)	162
I. Glucose-6-phosphate dehydrogenase (EC No. 1.1.1.49)	164
J. Xanthine dehydrogenase (EC No. 1.1.1.X)	164
K. 'Tetrazolium oxidase' (EC No. 1.?.?.?)	165
L. Catalase (EC No. 1.11.1.6)	166
IV. Transferases	167
A. Aspartate aminotransferase (= glutamate-oxaloacetate transaminase)	
(EC No. 2.6.1.1)	167
V. Hydrolases	167
A. Esterases (EC No. 3.1)	167
B. Alkaline phosphatase (EC No. 3.1.3.1)	168
C. Acid phosphatase (EC No. 3.1.3.2)	169
D. Peptidases (EC No. 3.4)	169
VI. Isomerases	170
A. Glucosephosphate isomerase (phosphohexoisomerase) (EC No.	
5.3.1.9)	170
CHAPTER 7. Protein Polymorphism—the Difficult Cases	
I. Isoalleles	171
A. Isoalleles of bovine transferrin and their association with milk	
production	171
B. Complex variation of egg white proteins of the quail, Coturnix	
coturnix	173
C. The common 'hidden' polymorphism of human haptoglobin and racial differences	1.7.4
	174
D. Estimates of the frequency of isoallelic variation—data from the human haemoglobins and from species comparisons	175
I Methods other than starch gal algotranhonaria for detection of must i	175
II. Methods, other than starch gel electrophoresis, for detection of protein polymorphism	1.77
	177
A. The use of reaction rates and equilibria to find allelic variation	177
1. Glucose-6-phosphate dehydrogenase of human erythrocytes	177
 Cholinesterase of human sera ('pseudocholinesterase') Haemoglobin variants 	177
	178
4. Enzymes which are electrophoretically distinct but isokinetic	179
B. Use of differential denaturation to find allelic variants	179
1. Isoalleles of bovine carboxypeptidase A	179
2. Isoalleles of esterase 6 ^F in <i>Drosophila</i> —the combination of heat	100
denaturation with electrophoresis	180
3. Heat sensitive human haemoglobin variants	180
4. Alkaline denaturation resistance of human foetal haemoglobin	180
C. Some other methods for the detection of allelic variation 1. Solubility	181
	181
 Microcomplement fixation and immunoelectrophoresis Peptide patterns ('fingerprinting') 	181
J. I optide patterns (iniger printing)	181

CONTENTS	xi
 Methaemoglobin—an example of the interaction of isoalleles, erythro- cyte enzymes and the environment A. Presence of excessive amounts of chemicals causing methaemoglobin 	182
formation	183
B. Defects in the methaemoglobin reductase system	183
C The abnormal haemoglobin M's	184
D The unstable haemoglobins—and interaction with drugs	185
E. Comparative aspects of methaemoglobinaemia	186
IV. Uninterpretable individual variation	187
A. Bad electrophoretic resolution	187
B. Physiological variation	187
C. Chemical modification	188
D. Interaction of genetic polymorphism with other aspects of protein	100
specificity	188
E. Permultiallelic protein polymorphisms	188
F. Some specific examples of unexplained individual variation	188
1. Seminal plasma proteins in the bull 2. 'Extra' zones of transferrin in the sprat and G_3 ovoglobulin in the	100
2. Extra zones of transferrin in the sprat and G ₃ ovoglobulin in the chicken	189
3. Serum esterases in the game pheasant	189
4. The strange case of haemoglobin of the spiny dogfish shark Squalus	190
4. The strange case of nacinogloom of the spiny dogish shark squams	170
CHAPTER 8. Some Examples of Hybrid Proteins, Positive Heterosis and Negative Heterosis	
I. Fish haemoglobins	193
A. Polymorphism of haemoglobin in the whiting, Gadus merlangus and	
the cod, G. morhua	193
B. Polymorphism of haemoglobin in the turbot, Scophthalmus maximus	198
C. Polymorphism of haemoglobin in the goby, <i>Gobius jozo</i>	200
D. Polymorphism of haemoglobin in the catfish, <i>Ictalurus sp.</i>	200
E. Hybrid haemoglobins of hybrid sunfish—the molecular basis of 'hybrid vigour'	202
II. Supergenes, and positive and negative heterosis in fish and fowl	202
A. Segregation of haemoglobin types in F_2 hybrid sunfish	207
B. Egg white proteins of the domestic fowl—negative heterosis and poor	200
hatchability	210
III. Genetic proletariats and genetic élites	215
A. Quail erythrocyte esterases, 6-phosphogluconate dehydrogenase	
(6-PG DH), glucose-6-phosphate dehydrogenase (G-6-P DH), and	
lactate dehydrogenase (LDH)	216
B. Polychaete Hyalinoecia tubicola 'nothing dehydrogenases'	223
CHAPTER 9. Quaternary Structure and Allosteric Effects	
I. The interrelation between heterosis, quaternary structure, allosteric	
effects, and control of metabolic pathways	226
II. Additional aspects of quaternary structure	228
A. Lability of the quaternary structure—formation of hybrid proteins	
in vitro	228
B. Genetic lability of the quaternary structure	230
1. General conditions for formation of a quaternary structure	230
 Polymerizing haemoglobins of mice and men Bovine β-lactoglobulin 	231
4. Haemoglobins from sibling species of sea cucumbers	231
5. Lactate dehydrogenases	233 233
denty di Ogenases	233

C. From quaternary structures to macromolecular ensembles—further consideration of haemoglobin and sickled erythrocytes	224
III. Allosteric effects	234
	235
A. Homointeractions and heterointeractions	235
B. An elementary algebra of allosteric effects	236
1. Homointeractions	236
2. The allosteric approximation (= 'Hill equation')	239
3. Heterointeractions	245
IV. Molecular basis and lability of the allosteric effects	247
A. Configurational changes	247
B. Properties and lability of allosteric effects	251
1. Most allosteric proteins have a quaternary structure	251
2. All four basic categories of homo- and heterointeractions occur,	
often in surprising variety in the same protein	252
3. The different allosteric effects within the same protein can frequently	
be separated	253
C. Genetic lability of allosteric effects	255
D. Diversity of allosteric effects	256
1. Coordinate feedback	256
2. Control of branching pathways—isozymes	257
3. Control of branching pathways—cumulative feedback inhibition	258
4. Multiple allosteric effects in haemocyanins	258
E. Substrate affinity, allosteric effects and temperature adaptation	259
CHAPTER 10. The Biochemical Basis of Positive and Negative Heterosis	
I. 'Hybrid vigour'	265
A. Some historical considerations	265
B. Hybrid proteins, allosteric effects, stability and heterosis	266
1. Hybrid haemoglobin of hybrid fish	266
2. NADP-dependent isocitrate dehydrogenase of the snail, Cepaea hortensis	267
3. Positive and negative 'hybrid vigour' in the isozymes of lactate	
dehydrogenase	267
C. Complementation at the level of different proteins	269
1. Abnormal human haemoglobins, glucose-6-phosphate dehydro-	
genase deficiency and malaria	269
2. Glycoproteins	270
3. Hybrid mitochondria of maize, Zea mays	270
4. Incompatibility as a source of negative or positive heterosis	270
II. General theory of positive and negative heterosis: complementation at the level of subunits and macromolecular ensembles	271
III. A partial correlation between hybrid zones in heterozygotes and 'hybrid	
vigour'	276
IV. Negative heterosis	282
A. Some examples of hybrid weakness	282
B. Possible benefits from negative heterosis	283
C. Mechanisms to avoid or to reduce negative heterosis	285
1. Supergenes	285
2. Sex linkage, Lyon effect and allelic exclusion-mechanisms to avoid	200
hybrid proteins?	286
3. Epistasis	287
4. Inbreeding	287
5. Null alleles and deletions	288

xii

CHAPTER 11. A Molecular Biology of Natural History—Application to the Study of Pollution and the Origin of Species	
time hybridization and habitat destruction	291
The astanoog H haradox III LIE Sulphul Outleting Cours cal finence	291
 A. The esterase E paradox in the estimate of the state of	294
C. Polymorphism and pollution	297
1. The dangers of pollution	297
2 Industrial melanism	298
3. Chromosomal polymorphism in Drosophila	299
4. A molecular biology of pollution	299
The origin of species	305
A. Negative heterosis as the internal driving force for speciation	305
p Can the theory be proven?	308
1. A deficit of heterozygotes should be most frequently found in assemblages which are currently evolving at a rapid rate—i.e.	309
 Comparison of related groups which are in different stages of speciation should reveal the greatest genetic asymmetry in those which have not yet broken up into species 	309
3. Other factors held constant, groups with moderately large numbers of zygotes per breeding pair will have the highest rates of speciation	310
4. Lowest rates of speciation should be found in the most uniform environments	311
5. A high rate of speciation occurs in tropical regions because of the necessity for positive heterosis in stabilizing proteins at higher temperatures, the diversity of ecological niches available, and the presence of small but predictable fluctuations in environmental	
factors 6. The rate of speciation, expressed per generation rather than per year,	311
should be much slower in forms where the majority of the life cycle is haploid	312
7. The rate of speciation is only indirectly related to the rate of mutation	313
CHAPTER 12. 'Hybrid Vigour' in Animal Breeding	214
I. Some relevant aspects of animal and plant breeding	314
A. Prehistoric and early historic breeding practice	314
B. The growth of the pedigree mystique	315
C. Hierarchical breed structure and 'grading up'	316
D. The use of genetic theory in animal breeding	317
E. Patterns and problems of breeding systems	318
F. Hybrid maize	320
G. The growth of the heterosis mystique	321
H. Problems in analysing the literature on 'hybrid vigour' in animal breeding	323
I. Commercial pressures	324
II. Some examples of positive and negative heterosis in animal breeding A. Interspecific bovine crosses	324 324
B. Beef cattle	326
 General aspects of 'hybrid vigour' from crossing beef breeds Muscular hypertrophy—the improvement of beef production and 	326
the import of the Charolais into the U.K.	327
C. Dairy cattle D. Sheep	330 333

xiii

CONTENTS

E. Pigs	20.5
F. Poultry	335
G. Fish	339
	349
III. Application of molecular biology to animal breeding	351
A. Removal of the mystique of heterosis	351
B. 'Gene-environment interaction'	352
C. The balance between natural and artificial selection	
D. Why the small breeder has not done so badly	354
E Why solution for the shot done so badly	354
E. Why selection for increased weight gain often results in increased	fat
rather than protein	355
F. Combination of molecular and mathematical methods	356
INDEX	
	381

xiv