Index

a
abscess formation 74
acanthosis 74
acetylcholinesterase 150
ACTH see adrenocorticotropic hormone
activated partial thromboplastin time (APTT) 126–127
acute-phase proteins 131–132
adenomatous hyperplasia 63–64
adrenocorticotropic hormone (ACTH) 101
adversity 145–156
   communicating NOAEL in toxicity studies 153–154
   concepts and definitions 145–146
   determining adversity using pathology findings 149–153
   functional effect 150–151
   LOEL, LOAEL, NOEL and NOAEL definitions 146–147
   pharmacological effect 153
   physiological adaptability 152
   primary versus secondary effects 151–152
   regulatory guidelines and definitions 147–149
   reversibility of lesion 152–153
   severity 149–150
alkaline phosphatase (ALP) isoenzyme 129
alopecia 73
alveolar macrophages 63, 87–88
amyloidosis 45
anatomic end points 168
anatomic pathology error 173–174
apoptosis 40–41
APTT see activated partial thromboplastin time
artefacts
   clinical pathology 113, 139–140
   pathology techniques 6, 8–9
   spontaneous and background lesions 61
atrophy 52–53
autolysis 4–5
b
background lesions see spontaneous and background lesions
basophils 122–123
benign tumours 54–55, 81–82, 103–104
bile 37
biologicals 19–20, 158
biomarkers 132
blind review 30
blocking sheets 7–8, 11–12
blood
   clinical pathology 113–131, 138–140
   coagulation 125–127, 140
   haematology 117–125
   urinalysis 140
body weight 136
bone marrow 125
bronchioloalveolar adenoma 88
calcification 38–39
calcium 130
carbohydrate metabolism 127–128
carcinogenicity 19, 31
cardiomyopathy 63, 160
cardiovascular system
  cardiac abnormalities 97–98
  developmental abnormalities 98
  target organ pathology 97–99
  vascular abnormalities 98–99
caseous necrosis 38–39
cassette label 7–8
cataracts 77–78
CD28 158
CD see clusters of differentiation
cellular responses to insults 35–41
central nervous system (CNS) 104–106
CF see cystic fibrosis
chemotaxis 42
chloride 130
cholesterol 37
chronic colitis 81
chronic progressive nephropathy (CPN) 29, 62–63, 68
circulatory disturbances
  clotting 49–51
  general pathology 47–51
  haemorrhage 50–51
  hydrothorax 48
  hyperaemia 46–47
  oedema 46–48
  petechiae 46, 48
clinical chemistry see serum chemistry analytes
clinical end points 168
clinical pathology 112–144
  acute-phase proteins 131–132
  analytic phase and data generation 114
  biomarkers 132
  coagulation 117, 125–127, 140
  concepts and definitions 112
  data analysis and interpretation 114, 134–135
  food consumption and body weight 136
  Good Laboratory Practice 114–115
  haematology 117–125, 138–139
  haemolysis and icterus 116, 119, 140
  instrumentation, validation and quality control 133–134
  lipaemia 116
  microsampling 140
  nonspecific change patterns 137
  organ weights 136
  postanalytic phase 114
  preanalytic phase and study plan 113–114
  reference intervals 133
  reporting 114, 135
  serum chemistry analytes 118, 127–131, 138
  serum and plasma 115–116
  study phases 112–114, 115
  typical profile changes in toxicology studies 136–140
  urinalysis 119, 131, 140
  variables for routine toxicology 116–119
  what is measured 115–117
  clotting 49–51
  clusters of differentiation (CD) markers 124
CNS see central nervous system
coagulation
  classic cascade model 125–126
  clinical pathology 125–127, 140
  standard coagulation profile 126–127
  variables for routine toxicology 117
coagulative necrosis 37–38
colitis 81
complement system 42–43, 56
confocal microscopy 16–17
congenital lesions 59–61
Congo red 12
conjunctivitis 76–77
constipation 81
continuous-infusion studies 18–19
contract research organisations (CRO) 23, 32
controlled terminology 26–27
CPN see chronic progressive nephropathy
CRO see contract research organisations
cystic fibrosis (CF) 165
d
  data analysis and interpretation 114, 134–135, 177–178
decalcification 13
dermatitis 41
Index

189
diagnostic drift 28
diarrhoea 80–81
DIC see disseminated intravascular coagulation
digital imaging 17
DILI see drug-induced liver injury
disseminated intravascular coagulation (DIC) 50
drug-induced liver injury (DILI) 159
dry gangrene 38, 40
dystrophic calcification 39
e
ear 106
efficacy/disease models 162–167
historical data 166
incompleteness in relation to human disease 165
interanimal variability and study size 165–166
limitations as toxicology models 164–167
nonregulated laboratory conditions 166–167
sensitivity 165–166
validation as safety/toxicity models 164–165
electrolytes 129–130
electron microscopy 15–16
embedding 9
EMH see extramedullary haematopoiesis
endocrine system
adrenal gland 101
malignancies 101–102
pituitary gland 100
target organ pathology 99–102
thyroid and parathyroid gland 100–101
Environmental Protection Agency (EPA) 148
enzymes 129
eosinophils 122–123
EPA see Environmental Protection Agency
epistaxis 51
euthanasia 4
exaggerated pharmacology 153
extramedullary haematopoiesis (EMH) 63–64
eye
cataracts 77–78
conjunctivitis 76–77
target organ pathology 76–78
f
FACS see fluorescence-activated cell sorting
fat necrosis 37, 39
FDA see Food and Drug Administration
fibrinogen 126–127
fibrinoid necrosis 38, 40
fibrinous inflammation 44, 45
fixation 5–6
fluorescence-activated cell sorting (FACS) 173
foamy macrophage accumulation 89
follicular destruction 73
food consumption 136
Food and Drug Administration (FDA) 147, 164
functional effect 150–151
g
GALT see gut-associated lymphoid tissue
gangrene 38, 40
gastrointestinal tract (GIT) 78–82, 131
general pathology 35–58
apoptosis 40–41
benign and malignant tumours 54
calcification 38–39
cellular responses to insults 35–41
circulatory disturbances 47–51
concepts and definitions 35
immune system 55–57
inflammation 41–47
leukocyte adhesion molecules 42–44
necrosis 36–41
neoplasia 54–55
reversible cell damage 36–37
severe cell injury 35–36
tissue growth disorders 52–53
tissue repair and healing 53–54
GFAP see glial fibrillary acid protein
GIT see gastrointestinal tract
glass slides
embedding 9
microtoming 9, 11
pathology techniques 6–12
quality control 11–12
Index

staining 9–10, 11
tissue processing 9, 10
tissue trimming 6–8
glial fibrillary acid protein (GFAP) 14
glomerulonephropathy 90–91
Good Laboratory Practice (GLP)
adversity 152
clinical pathology 114–115
limitations of pathology and animal models 166–167, 169
pathology techniques 4, 17–18, 20
recording pathology data 23, 32
grading schemes 25–26
granulocytes 122–123
granulomatous inflammation 45–46, 76
growth hormones 14
GALT (gut-associated lymphoid tissue) 95, 123–124

h
H&E see haematoxylin and eosin
haemangiosarcoma 99
haematocrit 119–120
haematology 117–125
bone marrow 125
haematocrit and red blood cell mass 119–120, 138–139
manual and automated techniques 118–119
platelets 124
red blood cells 120–122
standard haematology profile 124–125
variables for routine toxicology 117
white blood cells 122–124
haematopoiesis 61–62
haematoxylin and eosin (H&E) 10, 11, 170–172
haematuria 93
haemoglobin metabolism 129
haemolysis 116, 119, 140
haemorrhage 50–51
haemosiderin 37
harmonised nomenclature 26–27
HCD see historical control data
Health and Environmental Sciences Institute (HESI) 148–149
hepatitis 84
hepatocellular adenoma 84–85
HESI see Health and Environmental Sciences Institute
histopathology 169–170
historical control data (HCD) 30–32, 166
hyaline droplets 91
hydronephrosis 91–92
hydrothorax 48
hyperaemia 46–47
hyperostosis 96
hyperplasia 52, 80
hypersensitivity 56–57
hypertrophy
adversity 152
general pathology 52
target organ pathology 83–84, 88, 95–96, 100
hypoglycaemia 162, 163
hypotension 162
hypoxia 105–106

i
icterus 84–85, 116, 119
IHC see immunohistochemistry
image analysis 17, 170–173
immune system
general pathology 55–57
hypersensitivity 56–57
inflammation 57
innate versus adaptive immunity 55–56
limitations of pathology and animal models 163
immunohistochemistry (IHC) 13–14, 89, 170–172
infectious disease
adversity 151
spontaneous and background lesions 60–61, 67
target organ pathology 77, 78, 106
inflammation
actions of exudative phase 42
acute versus chronic
inflammation 44–46
amyloidosis 45
cells involved in 42–43
clinical signs 42
inflammation (Contd.)
complement system 42–43
functions of 45, 47
general pathology 41–47
granulomatous inflammation 45–46
immune system 57
spontaneous and background
lesions 65–66
target organ pathology 76–79, 83–84, 86–88
types of 44, 45
inhalation studies 18, 86
InHAND see International
Harmonization of Nomenclature
and Diagnostic
in situ hybridisation (ISH) 16, 170–172
instrument validation and
calibration 133–134
interanimal variability 165–166
International Harmonization of
Nomenclature and Diagnostic
(InHAND) criteria 27
International Programme on Chemical
Safety (IPCS) 149
interstudy/interlaboratory differences 170
IPCS see International Programme on
Chemical Safety
ischaemia 37, 38, 48–49
ISH see in situ hybridisation

j
jaundice 84–85

k
kidney 130–131

l
laboratory informatics management
systems (LIMS) 115, 134
laser capture microscopy 16
leiomyosarcoma 81, 82
leukocyte adhesion molecules 42–44
limitations of pathology and animal
models 157–183
anatomic and/or clinical end points 168
anatomic pathology error/missed
findings 173–174
causation or exacerbation of uniquely
human or undetectable
pathology 159
choice of study pathologist 176
concepts and definitions 157
efficacy/disease models as toxicology
models 162–167
hazards with no morphological
correlates 167
histopathology related to sampling
error 169–170
historical data 166
incompleteness of efficacy/disease
models 165
interanimal variability and study
size 165–166
in vivo animal models 157–162
preclinical safety studies 168
low incidence/low severity hazards 159
misinterpretation of reversibility/
recovery for low-incidence
findings 160
moribund animals/animals found dead
on study 168
nonregulated laboratory
conditions 166–167
over-/underestimation of spontaneous
pathology 160–161
pathology within in vivo toxicology
models 167–175
peer review 176–177
pharmacological activity of test
article 158
predictivity for aged/diseased human
populations 161–162
quantitative anatomic
pathology 170–173
review of anatomic pathology data 177
review of anatomic pathology data
interpretation 177–178
risk management 176–178
sensitivity of efficacy/disease
models 165–166
subjectivity and pathologist error 173,
176–178
subjectivity and pathologist
variability 175
traditional laboratory species and general toxicology models 157–158
validation of efficacy/disease models 164–165
LIMS see laboratory informatics management systems
lipaemia 116, 119
lipid metabolism 128–129
lipidosis 36–37
lipofuscin 37
liquefactive necrosis 37–38
liver
hypertrophy 83–84
malignancies 84–85
necrosis and inflammation 83–84
serum chemistry analytes 130
target organ pathology 83–85
livor mortis 5
lowest observable adverse effect level (LOAEL) 146–147
lowest observable effect level (LOEL) 146–147
lumping findings 29–30
lung inflation 5
lymph nodes 123–124
lymphocytes 123–124
lymphoma 64–65, 68
target organ pathology 83–85
liver necrosis
MCV see mean cell volume
mean cell haemoglobin concentration (MCHC) 122
mean cell volume (MCV) 119–122
metastatic calcification 39
MHC see major histocompatibility complex
microsampling 140
microtoming 9, 11
minerals 129–130
missed findings 173–174
monocytes 124
see also macrophages
moribund animals 168
mucosal-associated lymphoid tissue (MALT) 95, 123–124
multinucleate giant cells 45, 47
musculoskeletal system 95–97
n
NAD see nothing abnormal detected
nasal-associated lymphoid tissue (NALT) 87, 95
necropsy
general pathology 36–38
limitations of pathology and animal models 169–170
pathology techniques 2–5
spontaneous and background lesions 63–65
necrosis
general pathology 36–41
spontaneous and background lesions 66
target organ pathology 74–75, 83, 86, 92–93, 96
neoplasia
adversity 150
general pathology 54–55
recording pathology data 25
target organ pathology 80, 93
nephritis 41
nephrotoxicity 90
neutrophils 42–43, 122–123
NOAEL see no observable adverse effect level
NOEL see no observable effect level
nonsteroidal anti-inflammatory drugs (NSAID) 159
no observable adverse effect level (NOAEL) 146–147, 149, 153–154
no observable effect level (NOEL) 146–147
nothing abnormal detected (NAD) 26, 28–29
NSAID see nonsteroidal anti-inflammatory drugs

O
oedema 46–48
Oil Red O 12
organ weights 136
ovarian cysts 103–104

P
packed cell volume (PCV) 119–120
pancreatitis 81–82
papillary necrosis 92–93
parathyroid gland hyperplasia 97, 100–101
PAS see periodic acid–Schiff
pathologist error 173, 176–178
pathology findings see recording pathology data
pathology report 20
pathology techniques 1–22
animal considerations 2
artefacts 6
autolysis 4–5
biologicals 19–20
carcinogenicity 19
Cassette label and blocking sheet 7–8, 11–12
concepts and definitions 1–2
confocal microscopy 16–17
continuous-infusion studies 18–19
decalification 13
digital imaging 17
electron microscopy 15–16
euthanasia 4
fixation 5–6
glass slides 6–12
Good Laboratory Practice 4, 17–18, 20
image analysis 17
immunohistochemistry 13–14
inhalation studies 18
laser capture microscopy 16
lung inflation with fixative 5
macroscopic lesions 4
necropsy 2–5
pathology report 20
quality control 11–12
regulatory bodies 1, 17–18
in situ hybridisation 16
special histochemical stains 12–13
spermatocyte analysis 17
standard operating procedure 4, 18
study personnel 2
tissue crossreactivity 15
pathology working groups (PWG) 32
PCR see polymerase chain reaction
PCV see packed cell volume
peer review 32, 176–177
periodic acid–Schiff (PAS) 12
peripheral nervous system (PNS) 104–106
peritonitis 81
peroxisome proliferator-activated receptor (PPAR) 52
peroxisome proliferator-activated receptor (PPAR) agonists 13, 82, 87–88, 99
petechiae 46, 48, 75
phagocytosis 41–43
pharmacological effect 153
phaeochromocytoma 101–102
phospholipidosis adrenergic 150–151
pathology techniques 15
target organ pathology 89
phosphorus 130
phosphotungstic acid haematoxylin (PTAH) 12–13
photosensitivity 74
physiological adaptability 152
pituitary adenoma 100
platelets 124
pneumonia 88
PNS see peripheral nervous system
polymerase chain reaction (PCR) 16
polyp 81, 82
post mortem examinations see necropsy
potassium 130, 140
Index

PPAR see peroxisome proliferator-activated receptor
proliferative lesions 82, 84–85
protein metabolism 128
prothrombin time (PT) 126–127
pseudomelanosis 5
PT see prothrombin time
PTAH see phosphotungstic acid haematoxylin
purulent meningitis 36
pustules 74
PWG see pathology working groups
pyelonephritis 90–91

q
quality control 11–12, 133–134
quantitative anatomic pathology 170–173

r
RBC see red blood cells
RDW see red cell distribution width
recording pathology data 23–34
blind review 30
concepts and definitions 23
creation of a pathology term 27
diagnostic drift 28
grading schemes 25–26
historical control data 30–32
inconsistencies in pathology recording 28–30
lumping versus splitting 29–30
nomenclature/controlled terminology 26–27
ontological approach 28
pathology findings 24
peer review 32
semiquantitative analysis 24–26
standardisation of pathology findings 24–28
thresholds 28–29
red blood cell mass 119–120, 138–139
red blood cells (RBC) 119–122
red cell distribution width (RDW) 120–122
reference intervals 133
reporting 114, 135
reproductive system limitations of pathology and animal models 162
mammary gland changes 103–104
ovarian changes 103
spontaneous and background lesions 61
target organ pathology 102–104
testicular changes 102–103
uterus changes 103–104
respiratory system
inflammation 86–88
inhalation studies 86
macrophage aggregates 87–88
malignancies 87–88
phospholipidosis 89
pneumonia 88
target organ pathology 85–89
reticulocytes 120–121
reversibility of lesion 152–153, 160
rigor mortis 5
risk management 176–178
rotary microtome 9, 11

s
salivation 79
sampling error 169–170
scanning electron microscopy (SEM) 16
scarring 53–54
SEM see scanning electron microscopy
semiquantitative analysis 24–26
sensitivity 165–166
serum chemistry analytes 127–131
carbohydrate metabolism 127–128
common profile patterns 138
electrolytes and minerals 129–130
enzymes 129
haemoglobin metabolism 129
lipid metabolism 128–129
metabolites 127–129
protein metabolism 128
standard chemistry profiles 130–131
variables for routine toxicology 118
severity 149–150, 159
shock 51
sinus dilatation 174
skin
  acanthosis 74
  follicular destruction 73
  necrosis, erosion and ulceration 74–75
  petechiae 75
  target organ pathology 72–76
  topical xenobiotics 73–74
Society of Toxicologic Pathology (STP) 149, 151–153
sodium 130
SOP see standard operating procedure
spermatocyte analysis 17
spermatogenesis 66
splenomegaly 94
splitting findings 29–30
spontaneous alveolar macrophage aggregates 87–88
spontaneous and background lesions 59–71
artefacts 61
causes of death in rats and mice 67–69
concepts and definitions 59–62
congenital lesions 59–61
dogs 66
experimental procedures 67
haematopoiesis 61–62
infectious disease 60–61, 67
mice 63–65, 67–68
minipigs 66
non-human primates 67
rabbits 67
rats 62–63, 67–69
reproductive system 61
trauma 61, 65
squamous cell carcinoma 76, 78, 80
squamous cysts 59–60
squamous metaplasia 151
squamous papilloma 78–79
standard operating procedure (SOP)
  clinical pathology 114
  limitations of pathology and animal models 169–170
  pathology techniques 4, 18
  stomach ulceration 78–80
STP see Society of Toxicologic Pathology
stress response
  adversity 151–152
clinical pathology 139
spontaneous and background lesions 62
study plan 113–114
study size 165–166
subjectivity 173, 175–178
swallowing 79
target organ pathology 72–111
cardiocascular system 97–99
central and peripheral nervous system 104–106
concepts and definitions 72
ear 106
endocrine system 99–102
eye 76–78
gastrointestinal tract 78–82
liver 83–85
lymphoreticular system 94–96
musculoskeletal system 95–97
reproductive system 102–104
respiratory system 85–89
skin 72–76
urinary system 89–93
TCR see tissue crossreactivity
TEM see transmission electron microscopy
testicular disorders 162
TGN1412 158
thresholds 28–29
thromboelastography 126
thrombosis 49–50
thyroid-stimulating hormone (TSH) 84
tissue crossreactivity (TCR) 15
tissue growth disorders 52–53
tissue processing 9, 10
tissue repair and healing 53–54
tissue trimming 6–8
topical xenobiotics 73–74
tracheal instillation 5
transmission electron microscopy (TEM) 15–16
trauma 61, 65, 96–97
TSH see thyroid-stimulating hormone
TUNEL technique 40–41
type 2 diabetes 165
Index

u
ulcerative skin lesions 65
urinalysis
  blood in urine 140
  clinical pathology 119, 131, 140
  variables for routine toxicology 119
urinary system
  glomerulonephropathy 90–91
  hyaline droplets 91
  neoplasia 93
  nephrotoxicity 90
  papillary necrosis 92–93
  pyelonephritis 90–91
  stone and crystal formation 91–93
  target organ pathology 89–93
  tubular damage 89

v
validation 164–165
variability 175
vascular endothelial growth factor (VEGF) 53, 78

w
WBC see white blood cells
wet gangrene 38
white blood cells (WBC) 122–124
whole blood 113–114
within normal limits (WNL) 26, 28

x
xenobiotics 73–74, 80–81, 85–87, 89–90