

# Index

Note: page numbers in *italics* refer to figures and tables

- Acetaminophen, 126
  - glucuronidation, 125–8
  - glucuronide, 125, 128
- Acetate, carbon-labeled, 130
- Acetyl CoA, 132
- Acetylation, 131–2
- Acetylcholine, 291, 292, 294–5
- Acute insulin response (AIR), 10–11, 13
- Adipose tissue
  - lipolysis, 252
  - lipolysis tracers, 151–6
  - subcutaneous in insulin resistance
    - genesis, 252
- Adrenaline
  - glucose threshold for release, 94
  - hypoglycaemia studies, 89
  - measurement in hypoglycaemia studies, 93–4
- Adrenergic receptors, 79
- Adrenergic responses to hypoglycaemia, 80
- Adverse event reporting, 382–3
- Aging, 3
- Alanine, isotope labeling, 181
- Albumin
  - clearance, 345
  - excretion, 343–4
  - synthesis, 169
    - rate measurement, 182
- Allelic association, 368–9
- Alzheimer's disease, 368
- Amino acids
  - arterio-venous balance measurement, 177–8
  - black box model of metabolism, 174
  - compartmental models of balance in muscle, 178
  - hepatic glucose fluxes, 212
  - increased and insulin resistance, 203–4
  - kinetics, 169–86
  - leucine flux, 175
  - measurement approaches, 172–3
  - proteome dynamics, 181–2, 183–4
  - radioactive isotopes, 171–2
  - rates of flux, 174–5
  - stable isotopes, 171–2
  - tracers, 170–5
    - labeling, 173–4
    - tRNA-bound, 178, 180
    - turnover measurement, 170–5
- Anginal perceptual threshold, 315–16
- Animal models, hypoglycaemia studies, 96–7
- Apo  $\epsilon$ 4 allele, 368
- Applanation tonometry, 306
- Arginine tests, 16–17, 22
- Arterial compliance, 304–5
  - local, 306
- Arterial elasticity index, 305
- Arterial stiffness assessment, 303–7
  - advantages, 307
  - limitations, 307
  - local, 305–6
  - regional, 305
  - segmental, 305
  - systemic, 305
  - techniques, 305–6, 307
- Arteriovenous balance technique, 61
  - isotope tracers, 177–8
- Atherosclerosis, intima media thickness of carotid artery, 301, 302
- ATP synthesis, 205, 206
  - skeletal muscle, 250

- Bailey-Lovie chart, 358–9
- Baroreflex sensitivity, spontaneous, 320
- $\beta$ -cell function
- amplifying pathway, 11, 12
  - comparative evaluation of methods, 21, 22, 23–4
  - in vivo* assessment, 7–24
  - insulin sensitivity, 20–1
  - intravenous tests, 12–13, 21, 23
  - modeling, 18, 22
    - methods, 19–20
  - oral tests, 12–13, 23
  - tests, 12–19
  - triggering pathway, 11, 12
    - response in cellular processes, 11, 12
    - response in characteristics, 9–11
- Benzoic acid, 132–3
- Bergström needle, 266, 268
- Bioelectrical impedance analysis, 238–9
- Biopsies, 265–82, 282–4
- advantages, 270
  - applications, 270–3
  - complications, 269
  - discomfort, 269
  - freeze-drying of specimens, 270
  - limitations, 270
  - percutaneous needle of skeletal muscle, 266–7
  - procedure, 267–9
  - renal, 348
  - sample handling, 267–9, 270
  - skin, 335
  - sural nerve, 334–5
- Biopsy needle, suction, 266–7, 268
- Biopsy table, 268
- Biothesiometer, 331
- Blindness, 1
- Blood flow, forearm, 290–5
- Blood pressure measurement in hypoglycaemic studies, 93
- Blood sampling
- heated hand technique, 61
  - hyperinsulinaemic euglycaemic glucose clamp technique, 60–1
  - schedule, 64
- Bowman's space, 345
- Brachial artery
- diameter measurement, 299
  - flow mediated dilation, 295–9
  - strain gauge plethysmography, 295
- Brain
- glucose metabolism, 213–14
  - glutamate/glutamine neurotransmitter cycle, 214
  - magnetic resonance spectroscopy, 213–14
- C-peptide
- concentration, 19, 20
  - deconvolution, 8, 9, 15
  - exogenous insulin infusion effects, 56
  - graded glucose infusion test, 16
  - measurement, 8–9
  - model, 19, 20
- Calpain 10, 370
- Carbohydrate metabolism, xenobiotic probes, 125–33
- Cardiac studies
- PET imaging, 231–2
  - radionuclide imaging, 321, 322
- Cardiovascular autonomic function testing, 311–12, 322
- battery, 318–19
  - cardiac radionuclide imaging, 321, 322
  - reflex tests, 316–19
- Cardiovascular autonomic neuropathy (CAN), 311–12, 322
- clinical features, 313–16
  - diagnostic assessment, 316–21, 322
  - epidemiology, 312–13
  - prognosis, 312
  - spontaneous baroreflex sensitivity, 320
- Cardiovascular risk assessment, 300–1
- Carotid artery, intima media thickness, 299–303
- Cell cultures, 1
- Cerebral cortex, hypoglycaemia, 80
- Chemical shift imaging (CSI), 243, 247
- Choriocapillaris, 362–3
- Chylomicrons, 156–8, 159, 160, 164
- metabolism tracking, 157
- Clamping venous glucose concentration, 61
- Clinical research, 4
- regulatory legislation, 377–84
- Clinical trials
- adjudicated endpoints, 391
  - adverse events, 382–3
  - analysis, 392–3
  - bias sources, 391–2
  - biochemical measurements, 388–9, 392
  - clinical measurements, 388–9

- cross-over studies, 390
- data validation, 391
- demographics, 389
- error sources, 391–2
- informed consent, 380–1
- inspection, 383–4
- long-term studies, 390
- monitoring, 383–4
- outcome measures, 391
- outcomes for diabetes, 387
- patient variables, 389
- power calculations, 388
- protocols, 380–1
- publication bias, 378–9
- randomisation, 381
- regulatory legislation, 377–84
- reporting of study protocols, 390
- scientific misconduct, 378
- special populations, 381–2
- specialised designs, 390
- statistical considerations, 387–93
- study design, 388
- surrogate outcome measures, 391
- Cognitive impairment, diabetes mellitus
  - type 2, 213
- Cohen's kappa statistics, 388–9
- Cold thermal perception, 329
- Compartmental modeling, 225–6
- Complex diseases, gene associations, 373–4
- Compound muscle action potential, peak amplitude, 333
- Computed tomography (CT), 223
  - body fat measurement, 240–1, 242, 243
  - renal imaging, 347
- Conduction velocity distribution, 334
- Consent forms, 381
- CONSORT checklist/flowchart, 388, 389
- Continuous glucose monitoring, 84–5
- Convolution, 8
- Corneal confocal microscopy, 335–6
- Coronary artery disease, prevalence, 314
- Cortisol
  - glucose threshold for release, 94
  - hypoglycaemia studies, 87
  - measurement in hypoglycaemia studies, 93
- Counterregulatory hormones
  - glucose threshold for release, 94
  - measurement in hypoglycaemic studies, 93
- Creatinine clearance, 342, 343
- Creatinine, serum levels, 342, 343
- Cystatin C, 342, 343
- Cystic fibrosis, 367, 368
- Data analysis, 392–3
- Declaration of Helsinki (1964), 378
- Deconvolution, 8, 9, 15
- 2-deoxyglucose, 110
- Dextrans, 345
- Diabetes mellitus type 1 (T1DM)
  - continuous glucose monitoring, 84–5
  - endothelial dysfunction, 293
  - endothelial function, 297, 298
  - exercise, 297, 298
  - frequency, 368
  - hepatic glucose metabolism defects, 211
  - hypoglycaemia, 77
    - fatal, 78
  - intravenous insulin infusion test, 90
  - leucine flux, 175
  - lifestyle modification, 297, 298
  - protein turnover, 175
  - vascular function, 297, 298
  - weight reduction, 297
- Diabetes mellitus type 2 (T2DM), 1
  - calpain 10, 370
  - cognitive impairment, 213
  - endogenous glucose production, 114–17, 212
  - endothelial dysfunction, 292–3
  - executive function impairment, 213
  - frequency, 368
  - gene expression, 371, 372, 373
  - glucose intolerance, 117
  - glucose transport defects in muscle cells, 201
  - hepatic glucose metabolism defects, 211
  - insulin resistance, 265
  - insulin sensitivity and visceral fat content, 253
  - intima media thickness of carotid artery, 301
  - intramyocellular lipid content, 274
  - leucine flux, 175
  - markers, 270–1
  - molecular genetics, 367–75
  - muscle mitochondria, 274
  - polygenic inheritance, 367–75
  - protein turnover, 175

- Diabetes mellitus type 2 (T2DM) (*Continued*)
  - skeletal muscle
    - morphology, 273–6
    - oxidative capacity, 207
    - visceral fat content, 253
- Diabetes mellitus, forms, 387
- Diabetic autonomic neuropathy (DAN), 311
- Diabetic nephropathy
  - albumin excretion, 343–4
  - outcome measures, 391
  - renal genetic studies, 348
- Diabetic neuropathy, 311, 325–36
  - clinical assessment, 325–8
  - clinical screening devices, 328–30
  - signs, 327–8
  - symptoms screening questionnaires, 326
- Diabetic polyneuropathy (DPN), 325–36
  - axon reflex, 334
  - conduction velocity distribution, 334
  - corneal confocal microscopy, 335–6
  - electrophysiology, 332–4
  - excitability, 334
  - F-waves, 333–4
  - MRI, 335
  - non-invasive assessment, 335–6
  - peak amplitude, 333
  - quantitative sensory testing, 328, 329, 330–2
  - sural nerve biopsy, 334–5
  - thermal thresholds, 331–2
  - vibration perception threshold, 328–30
- Diabetic retinopathy
  - fluorescein angiography of fundus, 359–61
  - optical coherence tomography, 362–4
  - outcome measures, 391
  - retinal imaging, 364–5
  - screening, 357
  - visual acuity, 357–9
- Digital computerised imaging of retina, 364–5
- Disposition index, 21
- Drug administration, kidney function, 349
- Dual energy X-ray absorptiometry (DXA), body
  - fat measurement, 240, 241
- Dynamical diseases, 117
- Dyslipidaemia, 1
- Early Treatment Diabetic Retinopathy Study (ETDRS), 357
  - retinal imaging, 364
  - visual acuity chart, 359
- Edinburgh hypoglycaemia scale, 95
- Effective renal plasma flow (ERPF), 347
- Electrocardiogram (ECG), hypoglycaemic studies, 93
- Electromagnetic field, external pulsed, 198
- Electrophysiology, nerve function
  - testing, 332–4
- End-stage renal disease, 1
- Endocrine stimulation/suppression tests, 2
- Endothelial dysfunction, 290
  - strain gauge plethysmography, 292–3
- Endothelial function in diabetes mellitus type 1, 298, 297
- Ethics committees, 379–80, 381, 382
- Ethnic groups, 392
  - family-based association study, 371–2
- EudraVigilance database, 383
- Euglycaemic glucose clamp, *see*
  - Hyperinsulinaemic euglycaemic glucose clamp technique
- Excitation studies, 334
- Executive function impairment, diabetes mellitus type 2, 213
- Exercise
  - diabetes mellitus type 1, 298, 297
  - intolerance, 313–14
- Exercise tests, kidney function, 348
- Extramyocellular lipids, 244, 246
- Eye investigation techniques, 357–65
  - fluorescein angiography of fundus, 359–61
  - optical coherence tomography, 362–4
  - retinal imaging, 364–5
  - visual acuity, 357–9
- F-waves, 333–4
- Family-based association study, 371–2
- Family history, reporting, 392
- Fasting
  - glucose plasma levels, 145
  - glucuronide labeled water enrichment, 145
  - net glucose synthesis from hepatic G6P, 145–7
- Fat, body
  - bioelectrical impedance analysis, 238–9
  - content, 237–53
  - CT measurement, 240–1, 242, 243
  - distribution, 237–53
    - insulin resistance, 247–53
  - dual energy X-ray absorptiometry, 240, 241

- magnetic resonance imaging, 240–6
  - magnetic resonance spectroscopy, 241–7
  - measurement techniques, 237–46
  - ultrasonography, 239–40
  - visceral in insulin sensitivity, 253
  - whole body distribution, 252–3
- Fat free mass (FFM), 238–9
- Fatty acids
  - dietary, 157
  - see also* Free fatty acids
- Fed state, net glycogen synthesis from hepatic G6P, 147–8
- Ficoll 70, 345
- Flow mediated dilation of brachial artery, 295–9
  - advantages, 298
  - limitations, 298
  - procedure, 295–7
  - ultrasonography, 298, 299
- Fluorescein angiography of fundus, 359–61
- Food cravings, hypoglycaemia, 96
- Forearm blood flow (FBF), 290–5
  - oxidative stress, 293
  - simultaneous measurement in both arms, 292
- Free fatty acids
  - adipose tissue lipolysis, 252
    - tracers, 151–4, 155, 156
  - continuous tracer infusion, 153–4
  - determination methods, 152–3
  - gluconeogenesis, 212, 251
  - hepatic glycogen breakdown, 251
  - hepatic uptake, 230–1
  - labeled tracers, 151–4, 155, 156
  - oxidation, 154
  - skeletal muscle
    - ATP synthesis, 251
    - glucose transport impairment, 248
    - glucose uptake impairment, 202–3
    - uptake, 227
- FSIGT, 31
  - insulin-modified, 32, 33, 34
  - regular, 32, 33
  - tolbutamide-modified, 33
- Fundus photography with fluorescein, 359–61
- Gas chromatography–mass spectrometry, 141–2, 161
  - amino acid analysis, 171
- Gene association studies, 371–4
- Gene expression, 371, 372, 373
- Gene–environment interactions, 2
- Genetic risk, 367–8
- Genetic variability, 368–9
  - mapping, 368–75
- Genotyping, accuracy, 370
- Gestational diabetes, 185, 251, 389
- Gjedde-Patlak analysis, 226
- Glomerular basement membrane, 345
- Glomerular filtration
  - barrier charge, 344–5
  - rate measurement in clinical studies, 342, 343
  - size selectivity of barrier, 344–5
- Glomerular function, 341–2, 343
- Glomerular tubular balance, 346
- Glucagon
  - administration tests, 2
  - glycogen cycling role, 211
  - measurement in hypoglycaemia studies, 93
  - secretion response to hypoglycaemia, 79
- Glucagon-like peptide-1 (GLP-1), 9
- Glucagon-like peptide-1 (GLP-1) receptor
  - signaling, 18
- Gluconeogenesis
  - free fatty acids, 212, 251
  - glucose <sup>2</sup>H enrichment, 145–7
  - hepatic rate estimation, 129
  - rate, 2
  - whole-body glucose production, 209
- Glucose
  - basal conditions, 114–17
  - blood sampling, 60–1
    - schedule, 64
  - chemical analogues, 110
  - clamping venous concentration, 61
  - clearance, 31
  - concentration measurement, 61, 62–3, 63–4
  - continuous monitoring, 84–5
  - defective storage, 77
  - deuterated, 96
  - disposal rate, 37
  - efflux concentrations to liver, 107
  - endogenous output regulation, 55–6, 57
  - endogenous production, 108, 109, 110, 114–17, 122
    - compartmentalisation, 96
    - hepatic free fatty acids, 251–2
    - hepatic metabolic flux, 212
    - postprandial suppression, 118, 119
    - type 2 DM, 212
  - fasting production, 114
  - first-pass splanchnic uptake, 118

Glucose (*Continued*)

- flux
  - amino acid effects, 212
  - healthy liver, 207–10
  - skeletal muscle, 198–201
- flux rate measurement, 105–22
  - magnetic resonance spectroscopy, 198
- graded infusion test, 16, 22
- hepatic metabolism hormonal regulation, 211–12
- hepatic production, 29, 31
  - regulation, 55–6
  - stimulation by glucagon, 79
- hepatic production/uptake measurement, 106–7
  - glucose tracers, 107–11
  - influx concentrations, 107
  - systematic techniques, 110–22, 119
- hepatic utilisation, 127
- homeostasis, 28, 105, 117
- influx concentrations from liver, 107
- infusion rate, 52
  - adjustment, 61, 62–3, 63–4
- intolerance, 117
- intravenous infusions, 122
- intravenous tolerance index, 32
- isotope dilution technique, 57
- kinetics measurement, 96
- metabolic clearance rate, 53, 112, 113, 114, 115–16
  - peripheral insulin sensitivity, 117
- metabolism, 47–8, 49–54, 55, 57
  - brain, 213–14
  - defects in insulin resistance, 201–2
  - reproducibility of M value, 64
- myocardial metabolism, 231–2
- net splanchnic output, 106
- net synthesis from hepatic G6P, 145–7
- non-steady state, 112–14
- perturbed conditions, 117
- PET measurement of uptake, 227–8
- plasma concentration
  - clamp tests, 65
  - during fasting, 145
- postprandial fluxes, 117–18, 119
- potentiation slope, 17
- primers under basal conditions, 120–1
- rate of fall/recovery, 89–90
- skeletal muscle uptake, 202–3
- sources of errors, 118, 120
- specific activity clamping, 121
  - splanchnic extraction, 118
  - steady state, 28–9, 112
    - plasma levels, 30, 31
  - thresholds for hormone release, 94
  - tracing of hepatic, 139–48
  - utilisation, 29, 127
  - whole body metabolism (M value), 47–8, 49–54, 55, 57
    - insulin-stimulated, 54, 55
    - reproducibility, 64
  - see also* Intravenous glucose tolerance test (IVGTT); Oral glucose tolerance test (OGTT)
- Glucose-1-phosphate, 145
- Glucose-6-phosphate
  - hepatic, 142–4
  - net glucose synthesis, 145–7
  - net glycogen synthesis, 147–8
  - skeletal muscle, 199–200
  - transaldolase exchange, 144
- Glucose clamp techniques, 2, 27, 29, 43–68
  - insulin studies, 47–8
  - methodology, 57–61, 62, 63–4
  - one-step hyperinsulinaemic hypoglycaemia clamp study, 91
  - oral, 67
  - pancreatic, 66
  - somatostatin, 66
  - specific activity, 121
  - stepped hypoglycaemia clamp, 92
  - see also* Hyperglycaemic glucose clamp; Hyperinsulinaemic euglycaemic glucose clamp technique
- Glucose-dependent insulinotropic peptide (GIP), 9
- Glucose diaries, 81–3
- Glucose meals, 122
- Glucose meters, 87–8
  - hypoglycaemia, 81
- Glucose tolerance
  - impaired, 47
  - tests, 2
  - see also* Intravenous glucose tolerance test (IVGTT); Oral glucose tolerance test (OGTT)
- Glucose tracers, 96, 106–7
  - [1-<sup>14</sup>C], [6-<sup>14</sup>C], [1-<sup>13</sup>C] and [6-<sup>13</sup>C]glucose, 109–10
  - carbon-labeled, 109–10, 199–201
  - concentration response to infusion, 120–1
  - deuterated, 108–9

- distinguishability measurement, 107–8
- double tracer method, 117–18, 119
- equivalent entry, 111
- $^2\text{H}$  and  $^3\text{H}$ -labeled, 108, 109, 141–2
- [2- $^3\text{H}$ ] or [2- $^2\text{H}$ ] glucose, 108
- [6- $^3\text{H}$ ] or [6,6- $^2\text{H}_2$ ] glucose, 109
- [ $^2\text{H}_4$ -2,3,6,6] glucose, 109
- [3- $^3\text{H}$ ]glucose, 108–9
- intravenous infusions as meal surrogate, 122
- kinetic equivalence, 108–10
- labeled water, 108–9
- properties, 107–11
- quantitatively negligible, 110–11
- splanchnic uptake, 106, 108
- triple tracer technique, 122
- tritiated, 108–9
- [U- $^{13}\text{C}$ ] glucose, 110
- Glucose transport
  - defects in muscle cells, 201
  - impairment, 248
- Glucose transporters, 110–11
  - muscle fibre type expression, 275, 276
  - myotube cultures, 277
- Glucuronidation, 125–7, 128
- Glucuronide, 126
  - labeled water enrichment, 145
  - urinary sampling, 140–1
- GLUT1 myotube cultures, 277
- GLUT4
  - muscle fibre type expression, 275, 276
  - myotube cultures, 277
- Glutamate, 171–2
- Glutamate/glutamine neurotransmitter cycle, 214
- Glutamination, 128–30
- Glutamine, 128, 130, 214
  - brain levels in hypoglycaemia, 213
  - stable isotope studies, 172
- Glycaemic lability index, 83
- Glycerol, 155–6
- Glyceryltrinitrate, 294–5
- Glycination, 132–3
- Glycine, nitrogen isotope labeling, 176, 180
- Glycogen
  - cycling, 127, 145
    - glucagon role, 211
  - flux tracing, 139–48
  - hepatic, 207–8
    - breakdown with free fatty acids, 251
    - MRS quantification of synthesis, 209, 210
    - synthesis, 210, 212
    - net synthesis from hepatic G6P, 147–8
    - synthesis rate, 127
      - skeletal muscle, 201
- Glycogen synthase, 212
- Glycogenolysis, 2
  - hepatic glucose production, 209
  - MRS, 209, 210
- Glycosaminoglycans (GAGs), 345, 349
- Good clinical practice (GCP), 377–84
  - auditors, 383
  - inspection/monitoring, 383–4
- Graded glucose infusion test, 16, 22
- Growth hormone (GH)
  - glucose threshold for release, 94
  - measurement in hypoglycaemia studies, 93
- $^2\text{H}_2\text{O}$  stable isotope, *see* Water, labeled
- Haplotype blocks, 369
- HapMap project, 369
- HbA<sub>1c</sub> assays, 388, 390
- Heart rate
  - changes, 313, 314
  - circadian rhythms, 319, 321
  - measurement in hypoglycaemic studies, 93
  - power spectral analysis, 318, 319–20
- Heart rate variability (HRV)
  - 24-hour, 319–20
  - chaos dynamics, 320–1
  - correlation dimension analysis of
    - circadian rhythms, 321
    - non-linear analyses, 320–1
  - reduced, 312, 313, 314, 316–18
- Heated hand technique, 61
- Hepatic vein catheterisation
  - technique, 57
- Hexamethylenetetramine (HMT), 141
- Hippuric acid, 133
- HOMA method, 18–19, 22, 23, 37
  - indices, 21
- HOMA-R index, 29, 30
- Hunger in hypoglycaemia, 96
- [ $^{11}\text{C}$ ] hydroxyephedrine (HED), 321
- Hyperglycaemia, first phase insulin response, 10, 11
- Hyperglycaemic glucose clamp, 14–16, 21, 22, 37

- Hyperinsulinaemic euglycaemic glucose clamp technique, 37, 48–9
- blood sampling, 60–1
- endogenous glucose output regulation, 55–6
- glycaemic target nomenclature, 65–6
- insulin infusion, 58–60
- insulin sensitivity, 21
  - measurement, 44–5
  - reproducibility, 64
- M value calculation, 49–53
- methodology, 57–61, 62, 63–4
- principles, 49–57
- prolonged experiments, 53
- protocol modifications, 65–7
- safety, 65
- stepped, 67
- techniques used in combination, 57–8
- Hyperinsulinaemic hypoglycaemia clamp study, one-step, 91
- Hypoglycaemia
  - adrenergic responses, 80
  - animal studies, 96–7
  - autonomic symptoms, 94, 95
  - avoidance, 78
  - burden, 83, 84, 85
  - cerebral cortex inadequate fuel supply, 80
  - contraindications to, 85
  - cost of treatment, 78
  - counterregulation, 79, 80, 85
    - age/gender differences, 86
    - assessment methods, 77–9
    - hormonal response, 93
  - counterregulatory hormones
    - glucose threshold for release, 94
    - measurement, 93
  - definitions, 78–9
  - documentation, 81–5
  - duration, 85
  - episodes, 79
  - fatal, 78
  - food cravings, 96
  - frequency, 85
  - general malaise symptoms, 94, 95
  - glucagon secretion response, 79
  - glucose diaries, 81–3
  - glucose kinetics measurement, 96
  - glucose meters, 81
  - glucose sample, 87–8
  - glucose thresholds for hormone release, 94
  - hormone diurnal rhythms, 86
  - hunger, 96
  - hyperinsulinaemic euglycaemic glucose clamp technique, 65
  - iatrogenic, 77
  - insulin infusate, 88
  - insulin tolerance test, 89–90
  - intravenous insulin infusion test, 90
  - lability index, 83
  - neuroglycopenic symptoms, 95, 96
  - normoglycaemia prior to investigation, 86–7
  - one-step hyperinsulinaemic hypoglycaemia clamp study, 91–2
  - pathogenesis, 85–7
  - pathophysiology, 79–80
  - physiological response measurement, 93–7
  - questionnaires, 81–2, 83–4
  - recurrent, 78
  - safety issues in investigations, 85
  - scoring, 83
  - spontaneous, 78–9
  - stepped hypoglycaemia clamp, 92
  - stress hormones, 89
  - sulphonylurea-induced, 90–1
  - symptom measurement, 94–6
  - symptomatic response, 80
  - therapy target, 79
  - tolbutamide studies, 91
- Hypoglycaemia-associated autonomic failure (HAAF), 80
- Hypoglycaemia clamp, stepped, 92
- Hypoglycaemic stimuli for research, 89–93
- Hypokalaemia, hyperinsulinaemic euglycaemic glucose clamp technique, 65
- Hypotension, postural, 313, 314
  
- Imidazole acetic acid (IMA), 130–1
- Impaired glucose tolerance, insulin resistance, 47
- Independent ethics committees, 379–80, 381, 382
- Indocyanine green dye, 106
- Informed consent, 380–1
  - waiver, 381–2
- Inherited diseases, mapping, 368–75
- Institutional review boards, 379–80, 381, 382
- Insulin
  - clearance, 34
  - concentration, 8
  - defective secretion, 77
  - dose-response relationships, 48–9
  - endogenous secretion inhibition, 56

- first phase secretion, 10, 11, 13–14
- granules, 11, 12, 17
- hypoglycaemia induction, 89
- infusate, 88
  - preparation, 59–60
- infusion
  - hyperinsulinaemic euglycaemic glucose clamp technique, 58–60
  - intravenous test, 90
  - rate, 60
- plasma levels, 8
- responsiveness, 46–7
- secretion, 9, 10
- signaling cascade, 248
- in vivo* secretion, 7–9
- Insulin administration tests, 2, 90
- Insulin clamps, 122
- Insulin infusion test, intravenous, 90
- Insulin receptor substrate, s, Ierine
  - phosphorylation, 204
- Insulin resistance, 47
  - amino acid level increase, 203–4
  - body fat distribution, 247–53
  - definition, 27
  - disposition index, 21
  - hepatic, 30, 251–2
  - hepatic fat content, 251
  - HOMA method, 18–19
  - increased protein intake, 203–4
  - index, 29, 30
  - markers, 270–1
  - mitochondrial function, 205–7
  - myotube cultures, 281–2
  - skeletal muscle
    - biopsy, 271–3
    - glucose metabolism defects, 201–2
    - oxidative capacity, 207
    - T2DM marker, 270
    - tissue, 247
  - subcutaneous adipose tissue, 253
  - T2DM, 265
- Insulin sensitivity, 20–1, 27–38
  - definition, 45–6, 48
  - dynamic tests, 31–7
  - fasting measurements, 29–30, 44
  - indices, 30, 35, 44, 48
    - ISI<sub>comp</sub>, 35, 36
    - M value-derived, 53–4
    - MCR<sub>est</sub>, 35, 36
  - in vivo* assessment, 43–4
  - methods, 44–5
- M value, 47–8, 49–54, 55
- oral glucose tolerance test, 34–5
- peripheral, 117
- reproducibility from clamp tests, 64
- skeletal muscle ATP synthesis, 251
- steady-state tests, 28–31
- Stumvoll's method, 35, 36
- troglitazone, 202
- visceral fat content, 253
- Insulin suppression test, 29, 30–1, 37
  - quadruple infusion, 44
- Insulin tolerance test, 36–7, 38, 44
  - hypoglycaemia, 89–90
- International Conference on Harmonisation (ICH), 378, 384
- Intima media thickness of carotid artery, 299–303
  - advantages, 301–2
  - cardiovascular risk assessment, 300–1
  - limitations, 301–2
  - technique, 300, 302–3
- Intramyocellular lipid (IMCL) content, 205, 248–51
  - muscle fibre types, 275–6
  - regulation of stores, 250
  - T2DM, 274
- Intramyocellular lipids, 244, 246, 247–51
- Intravenous glucose tolerance index (K<sub>G</sub>), 32
- Intravenous glucose tolerance test (IVGTT), 9, 10, 13–14, 22, 31–4, 38
  - frequent sampling, 31, 32–4
  - minimal model, 32–3, 34
  - protocol, 32
  - rationale, 31–2
- Intravenous insulin infusion test, 90
- Inulin, glomerular filtration marker, 342, 343
- Investigational new drug (IND) sponsor, 382
- ISI<sub>comp</sub> insulin sensitivity index, 35, 36
- Isotope tracers
  - amino acids, 170–5
  - arteriovenous balance technique, 177–8
  - clearance with glomerular filtration, 342, 343
  - free fatty acids, 151–4, 155, 156
  - lipid kinetics, 156–8, 159, 160–4
  - lipolysis for adipose tissue, 151–6
  - metabolic imaging, 224
  - nitrogen balance coupling, 175–7
  - PET, 224, 225

- Isotope tracers (*Continued*)  
 protein kinetics, 173–4  
 rate of appearance (Ra), 172–3  
 rate of disappearance (Rd), 172  
*see also* Glucose tracers; Water, labeled
- $\alpha$ -ketoisocaproate, 179–80
- Kidney function, 341–50  
 albumin excretion, 343–4  
 functional MRI, 349, 350  
 genetic studies, 348  
 glomerular function, 341–5  
 MRS, 349  
 provocation tests, 348–9  
 renal haemodynamics, 346–7  
 renal structure, 347–8  
 renal tubular function, 346
- Kitt* (glucose disposal rate), 37
- Knockout mouse models, 1
- Lability index, 83
- Lactate, carbon-labeled, 130
- Left ventricular dysfunction, 314
- Leucine  
 flux studies, 175  
 tracer labeling, 173–4, 179–80
- Lifestyle modification, diabetes mellitus type 1,  
 298, 297
- Limb loss, non-traumatic, 1
- Linkage, 369–70
- Linkage disequilibrium, 368–9
- Lipid emulsions, artificial, 157–8, 159
- Lipid kinetics, 151–64  
 lipolysis tracers for adipose tissue, 151–6  
 tracers for triglyceride-rich lipoprotein  
 studies, 156–8, 159, 160–4
- Lipid oxidation pathway, skeletal  
 muscle, 250
- Lipid(s)  
 extramyocellular, 244, 246  
 hepatic, 252  
 intrahepatic, 250–1, 252  
 intramyocellular, 244, 246, 247–51  
 T2DM, 274  
 magnetic resonance spectroscopy,  
 243, 247  
 oxidation, 204  
 stored vesicles, 248
- Lipolysis tracers for adipose tissue, 151–6  
 free fatty acids, 151–4, 156  
 glycerol, 155–6
- Lipoprotein lipase (LPL), 155, 156, 157, 158,  
 160
- Lipoproteins, triglyceride-rich, 156–8, 159,  
 160–4
- Lithium clearance, 346
- Liver  
 acetaminophen glucuronidation, 125–6  
 fat  
 accumulation, 239–40, 243  
 content, 251  
 distribution maps, 245  
 free fatty acid uptake, 230–1  
 gluconeogenesis rate estimation, 129  
 glucose  
 flux, 207–10  
 production/uptake measurement, 106–7  
 utilisation, 127  
 glucose metabolism  
 defects, 211  
 hormonal regulation, 211–12  
 lipids  
 intrahepatic, 251, 252  
 quantification, 252  
 metabolic fluxes, 207–10  
 perturbation by substrate overabundance,  
 212  
 PET imaging of metabolism, 229–31
- LOD score, 369–70
- Lumped constant, 227
- M value, 81, 83  
 whole body glucose metabolism, 47–8,  
 49–54, 55, 57  
 insulin-stimulated, 54, 55  
 reproducibility of glucose values, 64
- Macroalbuminuria, 343, 344
- Macular degeneration, age-related, 359
- Macular oedema, diabetic, 361
- optical coherence tomography, 363–4
- Magnetic field, 193, 194  
 gradients, 195
- Magnetic resonance  
 frequency distribution, 195  
 safety hazards, 197  
 signal, 195  
 localisation, 197  
 signal-to-noise ratio, 195–6  
 specific absorption rate, 198
- Magnetic resonance imaging (MRI), 223  
 body fat measurement, 241–7  
 cine, 305, 306

- diabetic neuropathy, 335
- fat-selective, 246
- local arterial stiffness assessment, 305, 306
- phase-behaviour based contrast, 243
- renal imaging, 347
- T<sub>1</sub>-relaxation based contrast, 243
- Magnetic resonance imaging, functional (fMRI)
  - hypoglycaemia effects on brain, 213
  - kidney function, 349, 350
- Magnetic resonance spectroscopy (MRS), 2, 202–3
  - body fat measurement, 241–6
  - brain, 213–14
  - <sup>13</sup>C, 199–201
    - proton decoupled pulse sequences, 198
  - chemical shift imaging, 243, 247
  - glucose flux rate measurement, 198, 208–10
    - skeletal muscle, 198–201
  - <sup>1</sup>H, 213, 248
  - hepatic glycogen measurement, 207–8
  - information quantification, 196–7
  - kidney function, 349
  - metabolic flux assessment, 193, 194, 195–214
  - mitochondrial function, 205–7
  - <sup>31</sup>P, 199–201
    - proton decoupled <sup>13</sup>C pulse sequences, 198
  - renal imaging, 347
  - signal intensity conversion, 197
- Mass spectrometry, stable isotopes, 171
- Matsuda's formula for insulin sensitivity, 35, 36
- MCR<sub>est</sub> insulin sensitivity index, 35, 36
- Meal tests, 18
- Mean amplitude of glycaemic excursion (MAGE), 83
- Mendel errors, exclusion, 370
- Metabolic clearance rate (MCR) of glucose, 53, 112, 113, 114, 115–16
  - peripheral insulin sensitivity, 117
- Metabolic diseases, 1
- Metabolic flux perturbation and substrate overabundance, 202–4, 204–5
- Metabolic stimulation/suppression tests, 2
- Metabolic syndrome, 1
  - definitions, 3, 4
- Metaiodobenzylguanidine (MIBG), 321, 322
- 3-O-methylglucose, 110
- Micro aneurysms, diabetic retinopathy, 361
- Microalbuminuria, 343, 344
- β<sub>2</sub>-microglobulin, 346
- Mitochondria
  - function in insulin resistance, 205–7
  - genes regulating oxidative phosphorylation, 371
  - metabolism in skeletal muscle, 272–3
  - T2DM, 274
- Molecular genetics, 367–75
  - genetic variability mapping, 368–75
- Monoacetone glucose (MAG), 141–2
- Mortality, global, 1
- Mouse models, 1
- Muscle
  - compound action potential peak amplitude, 333
  - fibre types, 274, 275–6
  - vascular smooth muscle tone, 304
  - see also* Skeletal muscle
- Mydriatic digital photography, 365
- Myocardial infarction (MI), silent, 314–16
- Myocardial ischaemia, 314–16
- Myocardium, glucose metabolism, 231–2
- Myotube cultures, 276–82, 283–4
  - advantages, 279
  - applications, 281–2
  - cell culture principle, 277–9
  - limitations, 279–81
- N-acetyl glucosaminidase (NAG), 346
- L-NAME, 292
- Nerve conduction velocity (NCV), 330, 332–3
- Nerve function testing, 325–36
  - axon reflex, 334
  - clinical screening devices, 328–30
  - corneal confocal microscopy, 335–6
  - electrophysiology, 332–4
  - non-invasive assessment, 335–6
  - skin biopsy, 335
  - sural nerve biopsy, 334–5
- Neuron-specific enolase, 335
- Neuropen, 328
- NeuroQuick, 329
- Neurothesiometer, 329, 330
- Neurotransmitters, cycling, 214
- Nitric oxide, endothelium-derived, 295
- Nitric oxide synthase inhibitors, 292
- Nitrogen balance, isotope tracers, 175–7
- Nitrogen flux rate, 176
- L-NMMA, 292
- Noradrenaline, glucose threshold for release, 94

- Norepinephrine analogues, 321  
 Normoalbuminuric, 343, 344  
 Nuclear magnetic resonance (NMR)  
   <sup>2</sup>H glucose enrichment, 141–2  
   phenomena, 193, 194, 195–8  
   stable isotopes, 171
- Odds ratio, 374  
 OGIS model for insulin sensitivity, 35, 36  
 Oleate, carbon-labeled, 154, 155, 160  
 Optical coherence tomography (OCT), 362–4  
 Oral glucose clamp (OG-clamp)  
   techniques, 67  
 Oral glucose tolerance test (OGTT), 9, 10,  
   18, 22, 34–6, 38  
 Outcome measures, 391  
 Overexpression mouse models, 1  
 Oxidative phosphorylation, 371  
 Oxidative stress, vascular damage in  
   diabetes, 293
- Palmitate kinetics, 152–3  
 Perioperative instability, 316  
 PGC-1 $\alpha$  gene, 371, 372, 373  
 Phenylacetate, 128–30  
 Phosphate, inorganic, 205, 206  
 Phosphocreatine  
   brain levels in hypoglycaemia, 213  
   skeletal muscle pool, 205–7  
 Photodynamic therapy, 359  
 Plethysmography  
   venous occlusion, 291  
   *see also* Strain gauge plethysmography  
 Polyribosomes, protein profile, 185  
 Population attributable fraction (PAF), 368  
 Population attributable risk (PAR), 368  
 Positron emission tomography (PET), 2, 223–32  
   cardiac studies, 231–2  
   compartmental modeling, 225–6  
   FDG studies, 228–9  
   glucose uptake measurement, 227–8  
   graphical methods, 226–7  
   liver metabolism studies, 229–31  
   lumped constant, 227  
   regional perfusion measurement, 227–8  
   skeletal muscle metabolism assessment,  
     227–32  
   systemic substrate turnover, 227  
   tracers  
     kinetics, 225  
     metabolic imaging, 224  
     wash-out curve, 227
- Postural hypotension, 313, 314  
 Potassium, clamp tests, 65  
 Power calculations, 388  
 PPAR $\gamma$  gene, 368, 371, 372, 374–5  
 Prealbumin, synthesis studies, 180  
 Precursor:product-labeling techniques,  
   178–81
- Protein  
   arterio-venous balance measurement, 177–8  
   black box model of metabolism, 174  
   breakdown rate, 176  
   endogenous turnover, 176–7  
   gene transcription in control of dynamics, 185  
   homeostasis regulation, 177–8  
   increased intake and insulin resistance, 203–4  
   load in kidney function, 348–9  
   molecular control of dynamics, 185–6  
   polyribosome profile, 185  
   precursor:product-labeling techniques,  
     178–81  
   proteome dynamics, 181–2, 183–4  
   signal transduction cascades, 185  
   synthesis rate, 176  
     product-labeling techniques, 178–81  
   total excretion, 344  
   translation efficiency, 185  
   turnover measurement, 175–81  
   whole-body turnover determination, 174–5,  
     182, 184–5
- Protein gene product, 9.5 (PGP-9.5), 335  
 Protein kinetics, 169–86  
   approaches, 172–3  
   tracer labeling, 173–4  
 Proteinuria, 343, 344  
 Proteomes, dynamics, 181–2, 183–4  
 Publication bias, 378–9  
 Pulse pressure, 305, 306  
 Pulse-wave analysis, 303–4
- QT interval prolongation, 312  
 Quantitative sensory testing (QST) for  
   diabetic neuropathy, 328, 329, 330–2  
 Quantitative trait loci (QTL), 370  
 Questionnaires, hypoglycaemia,  
   81–2, 83–4  
 QUICKI, 37
- R-R intervals, 316–18, 320  
 Radioactive tracers, *see* Isotope tracers  
 Radiofrequency magnetic field, 193, 195  
 Radionuclide imaging, cardiac, 321, 322

- Randomisation, 381
- Rapamycin/S6 kinase 1 pathway, 204
- Renal
- blood flow, 347, 349
  - haemodynamics, 346–7
  - morphometry, 348
  - resistive index, 347
  - structure, 347–8
  - tubular absorption/reabsorption, 346
  - tubular function, 346
  - vascular resistance, 347
- Retina
- imaging, 364–5
  - thickness, 363–4
  - see also* Diabetic retinopathy; Macular oedema, diabetic
- Retinal pigment epithelium (RPE), 362–3
- Retinol binding protein, 346
- Ribosylimidazole acetic acid (IMAR), 130–1
- Riboxylation, 130–1
- Risk-to-benefit ratio, ethically acceptable, 379–80
- Rydel-Seiffer tuning fork, 328
- Satellite cells, 276
- human culture, 280
- Scientific misconduct, 378
- Semmes-Weinstein 10g monofilament (SWM), 328, 329
- Sensory nerve action potential, peak amplitude, 333
- Serious adverse event reporting, 382–3
- Sieving coefficient, 345
- Signal transduction, proteins, 185
- Single nucleotide polymorphisms (SNPs), 368–9, 370, 372
- haplotype tag, 373
- Single photon emission computed tomography (SPECT)
- cardiac imaging, 321, 322
  - MIBG, 321, 322
- Skeletal muscle
- ATP synthesis, 251
  - biopsies, 265–82, 282–4
  - capillary density, 274
  - fat distribution maps, 245
  - fixation, 273
  - free fatty acid uptake, 227, 248
  - gene expression, 371
  - glucose-6-phosphate, 199–200
  - glucose fluxes, 198–201
  - glucose metabolism defects in insulin resistance, 201–2
  - glycogen synthesis rate, 201
  - insulin resistance, 207, 247
    - biopsy, 271–3
    - glucose metabolism defects, 201–2
    - oxidative capacity, 207
    - T2DM marker, 270
    - tissue, 247  - intramyocellular lipids, 247–51
  - lipid accumulation, 204
  - lipid oxidation pathway, 250
  - metabolism assessment by PET, 227–32
  - mitochondrial metabolism, 272–3
  - morphology, 273–6
  - muscle fibre types, 274, 275–6
  - myotube cultures, 276–82, 283–4
  - oxidative capacity, 207
  - percutaneous needle biopsy, 266–7
  - phosphocreatine pool, 205–7
  - satellite cells, 276, 280
  - section preparation, 273
  - T2DM, 253
- Skin biopsy, 335
- Slit-lamp biomicroscopy, dilated, 365
- Snellen chart, 358
- Sodium clearance, 346
- Sodium fluorescein, 360–1
- Somatostatin, 335
- glucose clamp tests, 66
- Specific absorption rate (SAR), magnetic resonance, 198
- Strain gauge plethysmography, 290–5
- advantages/limitations, 293–4
  - vasoactive agents, 294–5
- Stress hormones, 89
- Substrate overabundance and perturbation of metabolic flux control, 202–4, 204–5
- Sulfamethazole, 131
- Sulphonylurea induced hypoglycaemia, 90–1
- Sural nerve biopsy, 334–5
- Sural/radial amplitude ratio (SRAR), 333
- Surrogate outcome measures, 391
- Suspected unexpected serious adverse event reaction (SUSAR), 382–3
- Sweating measurement in hypoglycaemic studies, 93
- Systemic substrate turnover, 227

- Tachycardia, resting, 313  
Tactile circumferential discriminator, 328  
Thermal thresholds, 331–2  
Thrifty genes, 373  
Tissue cultures, 1  
Tolbutamide, 33  
    hypoglycaemia studies, 91  
Total body water (TBW), 238–9  
Transaldolase exchange, 144  
Transmission disequilibrium test (TDT), 371–2  
Tremor measurement in hypoglycaemic studies, 93  
Tricarboxylic acid (TCA) cycle, 214  
Triglycerides  
    radiolabeled, 157, 158  
    stored lipid vesicles, 248  
Triolein, 163  
    labeled, 158  
Troglitazone, insulin sensitivity, 202  
Tubular protein excretion, 346
- UDPglucose, 125–6  
    flux, 127  
    oxidation, 145  
UDPglucuronic acid, 145  
UDPglucuronyl transferase, 125  
UKPDS  
    clinical measurements, 388–9  
    endpoints, 387, 391  
Ultrasonography  
    fat measurement, 239–40  
    flow mediated dilation of brachial artery, 298, 299  
    intima media thickness of carotid artery, 302  
    renal biopsy, 348  
    renal imaging, 347  
Urea  
    kinetics, 182, 184–5  
    recycling, 185  
    synthesis rate, 184–5
- Vascular damage, oxidative stress in diabetes, 293  
Vascular endothelium, 289–90  
    dysfunction, 290
- Vascular function, 289–308  
    arterial stiffness assessment, 303–7  
    diabetes mellitus type 1, 298, 297  
    flow mediated dilation of brachial artery, 295–9  
    intima media thickness of carotid artery, 299–303  
    strain gauge plethysmography, 290–5  
Vascular smooth muscle tone, 304  
Vasoactive agents for plethysmography, 291–2, 294–5  
Very low density lipoprotein (VLDL), 157, 158, 160–4  
    autologous tracers, 163  
    ex vivo preparation of tracers, 162–3  
    hepatic production, 160  
    labeling for intravenous administration, 162  
    triglyceride enrichment, 161  
Vibration perception threshold, 328–30  
Vibration thresholds, 328–30  
Visual acuity, 357–9  
Vitamin C, free oxygen radical scavenger, 293
- Wash-out curve, 227  
Water, body content, 140  
    bioelectrical impedance analysis, 238–9  
    steady state enrichment, 140  
Water, labeled  
    administration, 140–1  
    glucose tracers, 108–9  
    glycogen flux tracing, 139–48  
    <sup>2</sup>H<sub>2</sub>O stable isotope, 2  
    hepatic glucose tracing, 139–48  
    incorporation into hepatic  
        glucose-6-phosphate, 142–4  
    metabolite analyses, 141–2  
    precursor:product-labeling, 180–1  
Weight reduction, diabetes mellitus type 1, 297  
Western lifestyle, 1
- Xenobiotic probes of carbohydrate metabolism, 125–33  
    acetylation, 131–2  
    glucuronidation, 125–6, 128  
    glutamination, 128–30  
    glycination, 132–3  
    riboxylation, 130–1



