J. Fernandes · J.-M. Saudubray
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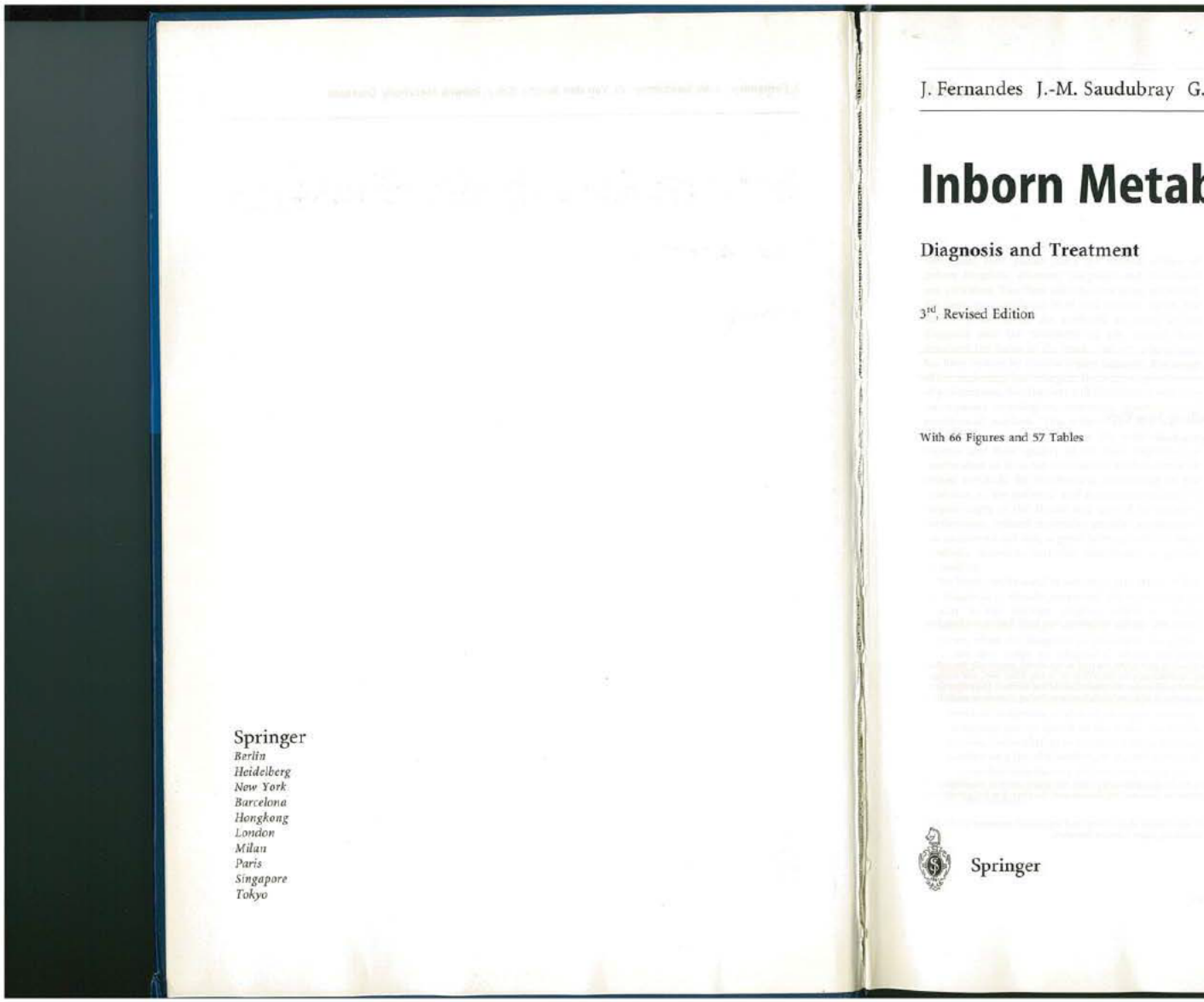
Editors

Inborn Metabolic Diseases

Diagnosis and Treatment

Third Edition

Springer



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3rd, Revised Edition

With 66 Figures and 57 Tables

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The Urea Cycle

The urea cycle which, in its complete form, is only present in the liver, is the main pathway for the disposal of excess of ammonium nitrogen. This cycle sequence of reactions, localised in part in the mitochondria and in part in the cytosol, converts the toxic ammonia molecule into the non-toxic product, urea, which is excreted in the urine. There are genetic defects of each of the enzymes of the urea cycle which lead to hyperammonaemia. Some genetic defects of other important metabolic pathways may lead to secondary inhibition of the urea cycle. Alternative pathways for nitrogen excretion, namely conjugation of glycine with benzoate and of glutamine with phenylacetate can be exploited in the treatment of patients with defective ureagenesis.

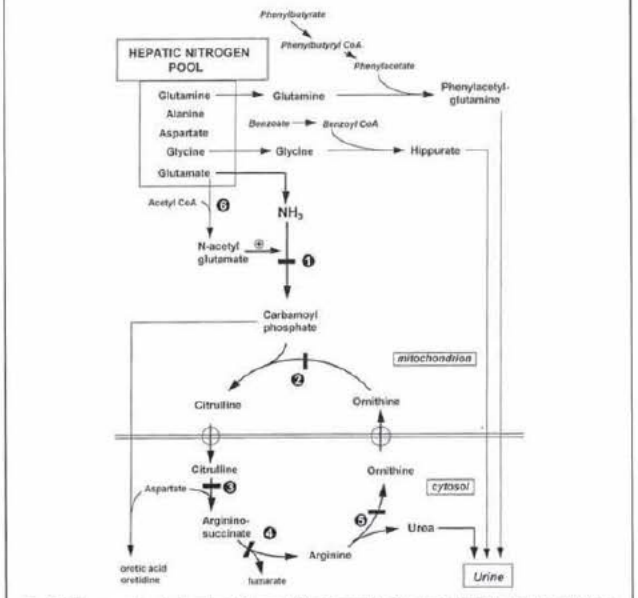

Fig. 17.1. The urea cycle and alternative pathways of nitrogen excretion. Enzymes: 1, carbamoyl phosphate synthetase; 2, ornithine transcarbamoylase; 3, argininosuccinate synthetase; 4, argininosuccinate lyase; 5, arginase; 6, N-acetylglutamate synthetase. Enzyme defects are depicted by *solid bars* across the arrows

CHAPTER 17

Disorders of the Urea Cycle

J.V. Leonard

CONTENTS

Five inherited disorders of the urea cycle are now well described. These are characterised by hyperammonaemia and disordered amino-acid metabolism. The presentation is highly variable: those presenting in the newborn period usually have an overwhelming illness that rapidly progresses from poor feeding, vomiting, lethargy or irritability and tachypnoea to fits, coma and respiratory arrest. In infancy, the symptoms are less severe and more variable. Poor developmental progress, behavioural problems, hepatomegaly and gastrointestinal symptoms are usually observed. In children and adults, chronic neurological illness is characterised by behavioural problems, confusion, irritability and cyclic vomiting, which deteriorates to acute encephalopathy during metabolic stress. Arginase deficiency shows more specific symptoms, such as spastic diplegia, dystonia, ataxia and fits. All urea-cycle disorders have autosomal-recessive inheritance except ornithine carbamoyl transferase deficiency, which is X-linked.

mia, apnoea and fits. The baby may soon become totally unresponsive and may require full intensive care. Untreated, most babies will die, often with complications, such as cerebral or pulmonary haemorrhage, the underlying metabolic cause for which may not be recognised. Some survive neonatal hyperammonaemia but are invariably handicapped to some degree.

Infantile Presentation

In infancy, the symptoms are generally rather less acute and more variable than in the neonatal period and include anorexia, lethargy, vomiting and failure to thrive, with poor developmental progress. Irritability and behavioural problems are also common. The liver is often enlarged but, as the symptoms are rarely specific, the illness is initially attributed to many different causes that include gastrointestinal disorders (gastro-oesophageal reflux, cow's milk protein intolerance), food allergies, behaviour problems or hepatitis. The correct diagnosis is often only established when the patient develops a more obvious encephalopathy with changes in consciousness level and neurological signs (see below).

Children and Adults

At these ages, the patients commonly present with a more obviously neurological illness.

ACUTE ENCEPHALOPATHY. Whilst older patients often present with episodes of acute metabolic encephalopathy, they may also have chronic symptoms. Usually, symptoms develop following metabolic stress precipitated by infection, anaesthesia or protein catabolism, such as that produced by the rapid involution of the uterus in the puerperium [1]. However an obvious trigger is not always apparent. The patients first become anorexic, lethargic and unwell. Sometimes they are agitated and irritable, with behaviour problems or confusion. Vomiting and headaches may be prominent, suggesting migraine or cyclical vomiting. Others may be ataxic as though intoxicated. On examination, hepatomegaly may be present, particularly in those with argininosuccinic aciduria. The patients may then recover completely but, if not, they may then develop neurological problems, including a fluctuating level of consciousness, fits and (sometimes) focal neurological signs, such as hemiplegia [2] or cortical blindness. Untreated, they continue to deteriorate, becoming comatose, and they may die. Alternatively, they may recover with a significant neurological deficit. The cause of death is usually cerebral oedema.

Between episodes, the patients are usually relatively well, although some, particularly younger ones, may continue to have problems, such as vomiting or poor developmental progress. Some patients may voluntarily restrict their protein intake. In addition to those disorders already mentioned, the illness may be attributed to a wide variety of other disorders, including Reye's syndrome, encephalitis, poisoning and psychosocial problems.

CHRONIC NEUROLOGICAL ILLNESS. Learning difficulties or more obvious mental retardation are common, and some patients, particularly those with argininosuccinic aciduria, may present with relatively few symptoms apart from mental retardation and fits. About half the patients with argininosuccinic acid have brittle hair (trichorrhexis nodosa). Patients may present with chronic ataxia, which is worse during intercurrent infections [3].

ARGINASE DEFICIENCY. Arginase deficiency commonly presents with spastic diplegia and, initially, a diagnosis of cerebral palsy is almost always suspected. However, the neurological abnormalities appear to be slowly progressive, although it may be difficult to distinguish this from an evolving cerebral palsy. During the course of the disease, fits, ataxia and dystonia may develop. Occasionally, patients may present with an acute encephalopathy or anticonvulsant-resistant fits [4].

Metabolic Derangement

The urea cycle is the final common pathway for the excretion of waste nitrogen in mammals. The steps in the urea cycle are shown in Fig. 17.1. Ammonia is probably derived principally from glutamine and glutamate and is converted to carbamoyl phosphate by *carbamoyl phosphate synthetase* (CPS). This enzyme requires an allosteric activator, *N*-acetylglutamate, for full activity. This compound is formed by the condensation of acetyl coenzyme A (acetyl CoA) and glutamate in a reaction catalysed by *N-acetyl glutamate synthetase*. Carbamoyl phosphate condenses with ornithine to form citrulline in a reaction catalysed by *ornithine transcarbamoylase*. The product, citrulline, condenses with aspartate to produce argininosuccinate in a reaction catalysed by *argininosuccinate synthetase*, and the argininosuccinate is then hydrolysed to arginine and fumarate by *argininosuccinate lyase*. The arginine is itself cleaved by *arginase*, releasing urea and re-forming ornithine. Within the urea cycle itself, ornithine acts as a carrier; it is neither formed nor lost.

Each molecule of urea contains two atoms of waste nitrogen, one derived from ammonia and the other from aspartate. Regulation of the urea cycle is not fully understood, and it is likely that there are several mechanisms controlling flux through this pathway [5].

These include enzyme induction, the concentrations
substrates, intermediates and *N*-acetyl glutamate,
hormonal effects. Defects of each step have now be
described and are listed in Table 17.1.

The plasma *ammonia* concentration is raised a
result of metabolic blocks in the urea-cycle. The deg
to which it is elevated depends on several facto
including the enzyme involved and its residual activi
the protein intake and the rate of endogenous prot
catabolism, particularly if this is increased because
infection, fever or other metabolic stresses. The val
may also be falsely elevated if the specimen is
collected and handled correctly.

The concentrations of the amino acids in
metabolic pathway immediately proximal to the
zyme defect will increase, and those beyond the blo
will decrease (Table 17.1). In addition, plasma alani
and particularly *glutamine* accumulate in all
disorders. The concentration of *citrulline* is oft
helpful, but it may not always be reliable during
newborn period [6].

Orotic acid and orotidine are excreted in excess
the urine if there is a metabolic block distal to
formation of carbamoyl phosphate, as is the case
ornithine transcarbamoylase (OTC) deficiency,
rullinaemia, argininosuccinic aciduria and argina
deficiency (Fig. 17.1). In these disorders, carbam
phosphate accumulates, leaves the mitochondrion a
once in the cytosol, enters the pathway for the de no
synthesis of pyrimidines. The urea cycle is also clos
linked to many other pathways of intermedia
metabolism, particularly the citric-acid cycle.

Toxicity

Ammonia increases the transport of tryptophan acro
the blood–brain barrier, which then leads to
increased production and release of serotonin [

Table 17.1. Urea-cycle disorders: biochemical and gen

Disorder	Alternative names	Plasma amino acid concentrati
CPS deficiency	CPS deficiency	↑ Glutamine; ↑ al ↓ citrulline; ↓ ar
OTC deficiency	OTC deficiency	↑ Glutamine; ↑ al ↓ citrulline; ↓ ar
Argininosuccinic synthetase deficiency	Citrullinaemia	↑↑ Citrulline; ↓ a
Argininosuccinic lyase deficiency	Argininosuccinic aciduria	↑ Citrulline; ↑ argininosuccini ↓ arginine
Arginase deficiency	Hyperargininaemia	↑ Arginine
NAGS deficiency	NAGS deficiency	↑ Glutamine; ↑ al

↑, increased; ↓, decreased; *AR*, autosomal recessive; *CPS*, synthetase; *OTC*, ornithine transcarbamoylase; *RBC*, red blood

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