Pyrimidin-5`-Nucleotidase-Mangel - eine unterschätzte Erkrankung?

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Hereditary Hemolytic Anemia with Human Erythrocyte Pyrimidine 5′-Nucleotidase Deficiency

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ABSTRACT A severe deficiency of a red cell pyrimidine 5′-nucleotidase was found to be associated with hereditary hemolytic anemia in four members of three kindreds. The syndrome was characterized by marked increases above normal in red cell basophilic stippling, total nucleotides, and GSH and by a fairly severe deficiency of ribosephosphate pyrophosphokinase (EC 2.7.-6.1.). Patient erythrocytes uniquely contained large amounts of pyrimidine 5′-ribonucleotides. In earlier studies, these were erroneously considered to be adenosine phosphates, since all previous investigations of the nucleotides of human red cells and reticulocytes have shown 97% or more to contain adenine. Total nucleotides in patient cells were present in amounts 3–6 times greater than normal, and approximately 80% contained pyrimidine. The ultraviolet spectral curves of deproteinized red cell extracts exhibited a shift in maximum absorbance from the usual 256–257 nm to approximately 266–270 nm, and absorbance at 250, 270, 280, and 290 nm, expressed as a ratio of that at 260 nm, differed greatly from normal. The spectral characteristics of extracts provide the basis of a readily performed screening procedure, which does not require enzyme assay. The nucleotidase activity in deficient red cells assayed less than 14%, and usually less than 10%, of normal and much less in terms of reticulocyte-rich blood, where it was consistently found to be increased. The enzyme has a pH optimum of 7.5–8.0, is inhibited by EDTA, and does not utilize purine 5′-ribonucleotides or β-glycerophosphate as substrates. While comparatively few family members have been available thus far for study, initial data are compatible with an autosomal, recessive mode of transmission of the deficiency. The pyrimidine 5′-ribonucleotides are presumably derived from RNA degradation and, not being diffusible, accumulate when the enzyme catalyzing their dephosphorylation is deficient. It is postulated that the prominent basophilic stippling results from retarded ribosomal RNA degradation secondary to accumulation of degradation products, namely pyrimidine 5′-ribonucleotides. Ribosephosphate pyrophosphokinase deficiency is considered to be an epiphenomenon. The mechanism responsible for increased red cell GSH is unknown.

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INTRODUCTION

In 1972–73, this laboratory reported four subjects with hereditary nonspherocytic hemolytic anemia associated with increased red cell adenine nucleotides GSH, and basophilic stippling, and a fairly severe, though partial, deficiency of ribosephosphate pyrophosphokinase (RPK,[1] 5-phosphoribosyl-1-pyrophosphate synthetase, EC 2.7.-6.1.) (1, 2). In these studies, AMP, ADP, and ATP were measured by a conventional enzymatic procedure (3). The assay had been considered reliable, since normally 97% or more of the nucleotides of both human red cells and reticulocytes are adenosine phosphates (3–11). Nucleotides containing guanosine may range in amount from less than 1 to 3%, and pyrimidine-contain-

[1] *Abbreviations used in this paper:* AK, adenylate kinase; EU, enzyme units; LDH, lactate dehydrogenase; NDPK, nucleoside diphosphate kinase; NMPK, nucleoside monophosphate kinase; PCA, perchloric acid; PEP, P-enolpyruvate; PGK, phosphoglycerate kinase; PK, pyruvate kinase; PRPP, 5-phosphoribosyl-1-pyrophosphate; RBC, erythrocytes; RPK, ribosephosphate pyrophosphokinase; TCA, trichloroacetic acid; TEA, tetraethylammonium.

Pyrimidin-5`-Nucleotidase-Mangel
- Fallbericht -

11 jähriges Mädchen

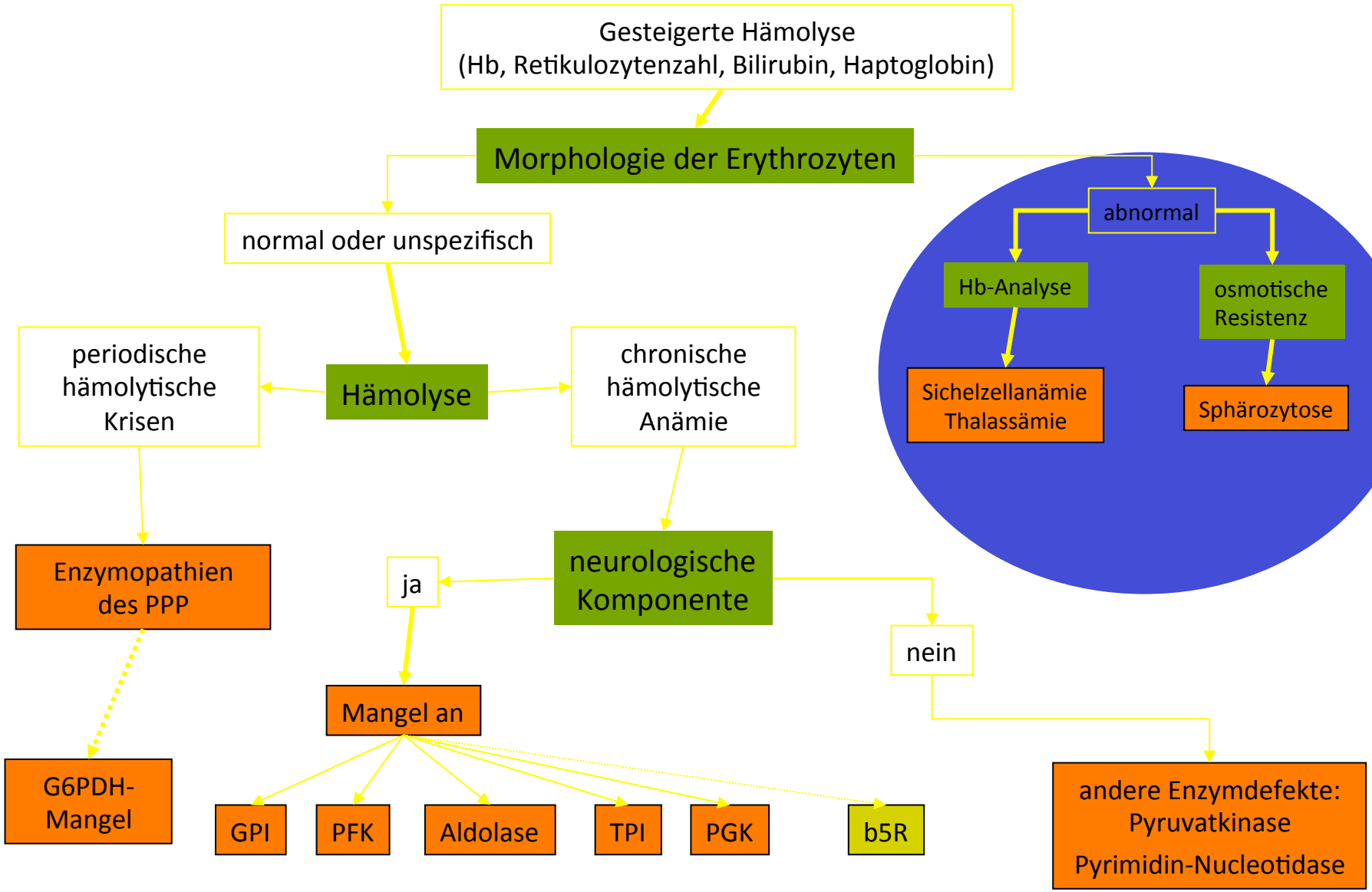
Anamnese: seit langem Ikterus und Blässe, Familienanamnese unauffällig

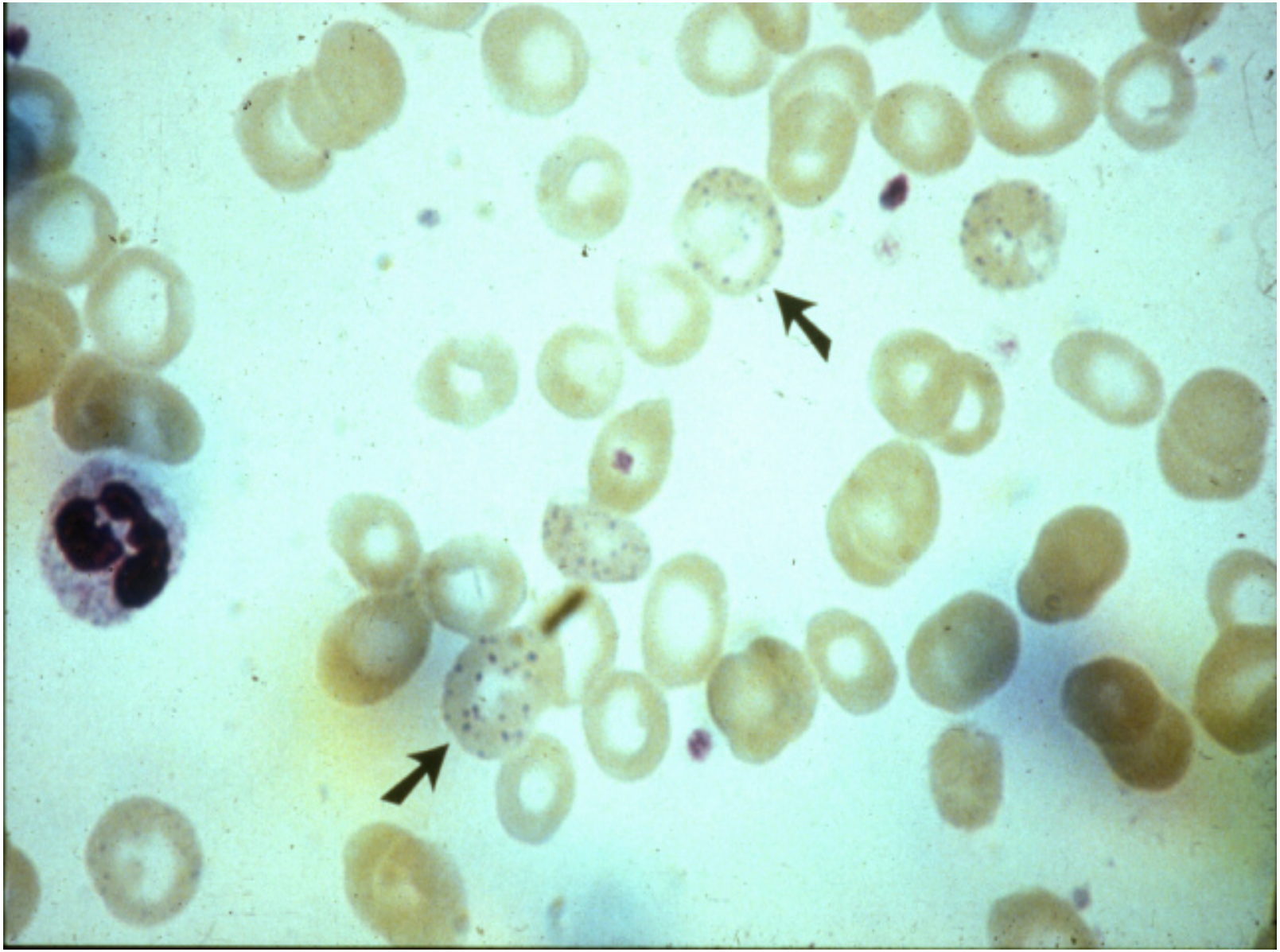
Befund: altersentsprechend, Ikterus, Blässe, Milz gering vergrößert

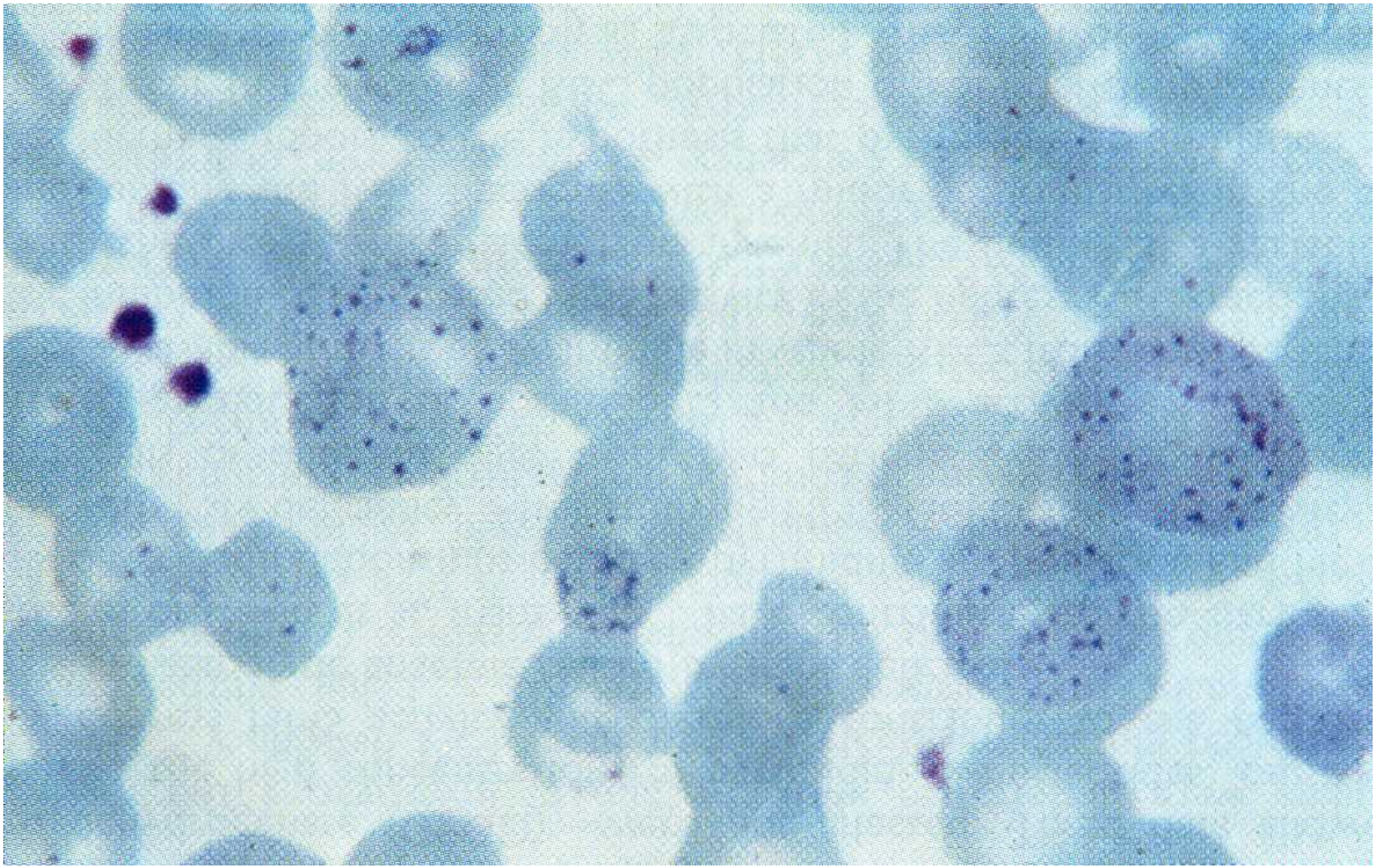
Labor: Hb 11,5 g/dl,
MCV 80 fl,
Retikulozyten 7%
Haptoglobin < 0,1 g/l,

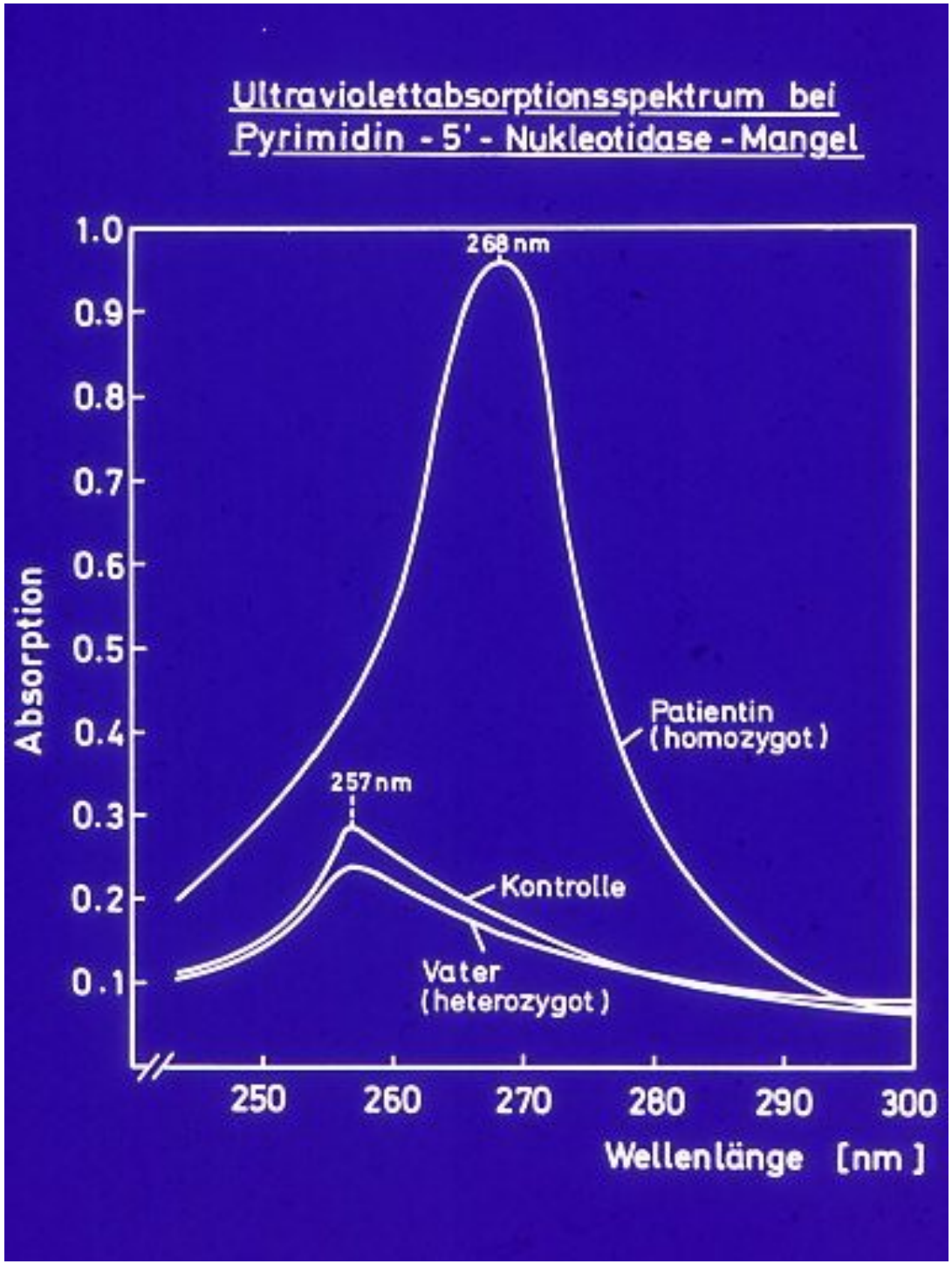
Osmotische Fragilität normal
Pyruvatkinase-Aktivität normal
Glucose-6-Phosphat-Dehydrogenase-Aktivität normal
Hämoglobin-Elektrophorese unauffällig

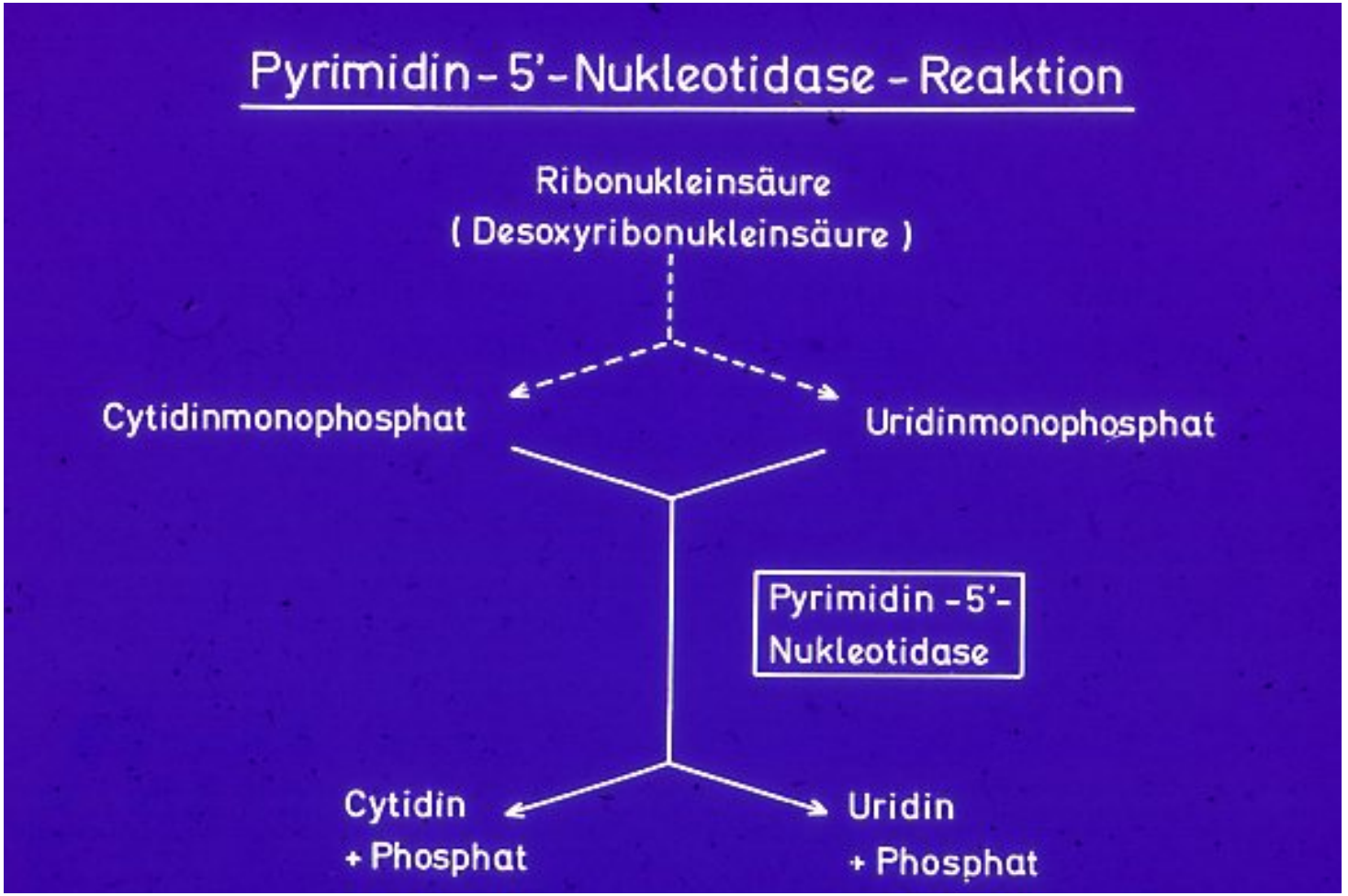
Differentialdiagnose bei genetisch bedingten hämolytischen Anämien








Ultraviolettabsorptionsspektrum bei
Pyrimidin - 5' - Nukleotidase - Mangel
Absorption
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
268 nm
257 nm
Patientin
(homozygot)
Kontrolle
Vater
(heterozygot)
250
260
270
280
290
300
Wellenlänge [nm]


Pyrimidin-5'-Nukleotidase-Reaktion
Ribonukleinsäure
(Desoxyribonukleinsäure)
Cytidinmonophosphat
Uridinmonophosphat
Pyrimidin-5'-
Nukleotidase
Cytidin
+ Phosphat
Uridin
+ Phosphat

Pyrimidin-5`-Nucleotidase
- Merkmale-

Mitglied einer „Nucleotidasen-Familie“

Cytosolisch lokalisiert

Expression in Erythrozyten (und in anderen Zelltypen)

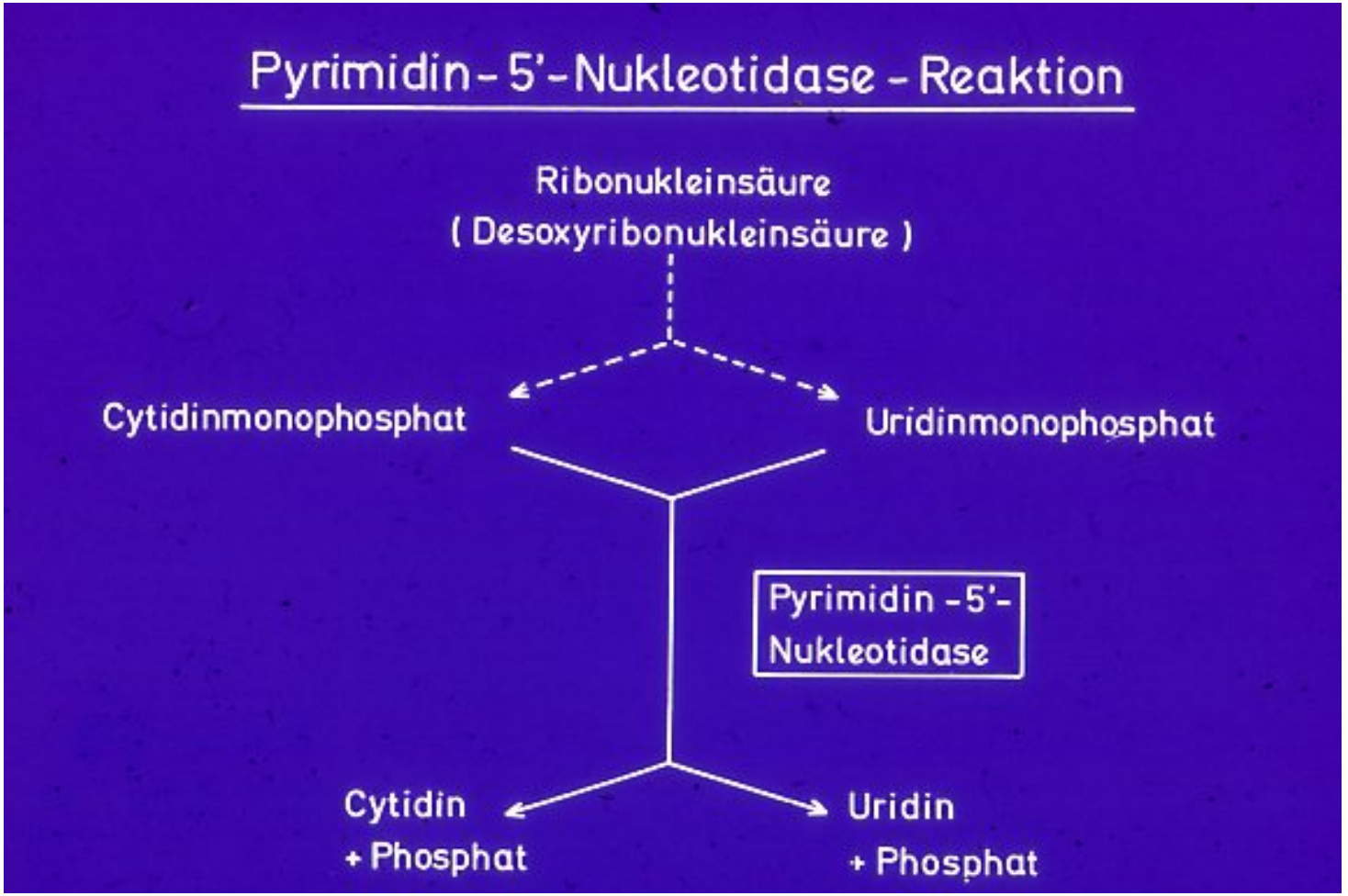
Enzymaktivität in Retikulozyten erhöht

Spezifität für Pyrimidin-Nucleotide

Aktivitäts-Hemmung durch Blei

Molekulargewicht 45 KD

Chromosom 7p15 - p14


Pyrimidin-5'-Nukleotidase-Reaktion
Ribonukleinsäure
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Cytidinmonophosphat
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Pyrimidin-5'-
Nukleotidase
Cytidin
+ Phosphat
Uridin
+ Phosphat

Pyrimidin-5`-Nucleotidase-Mangel
- Pathophysiologie -

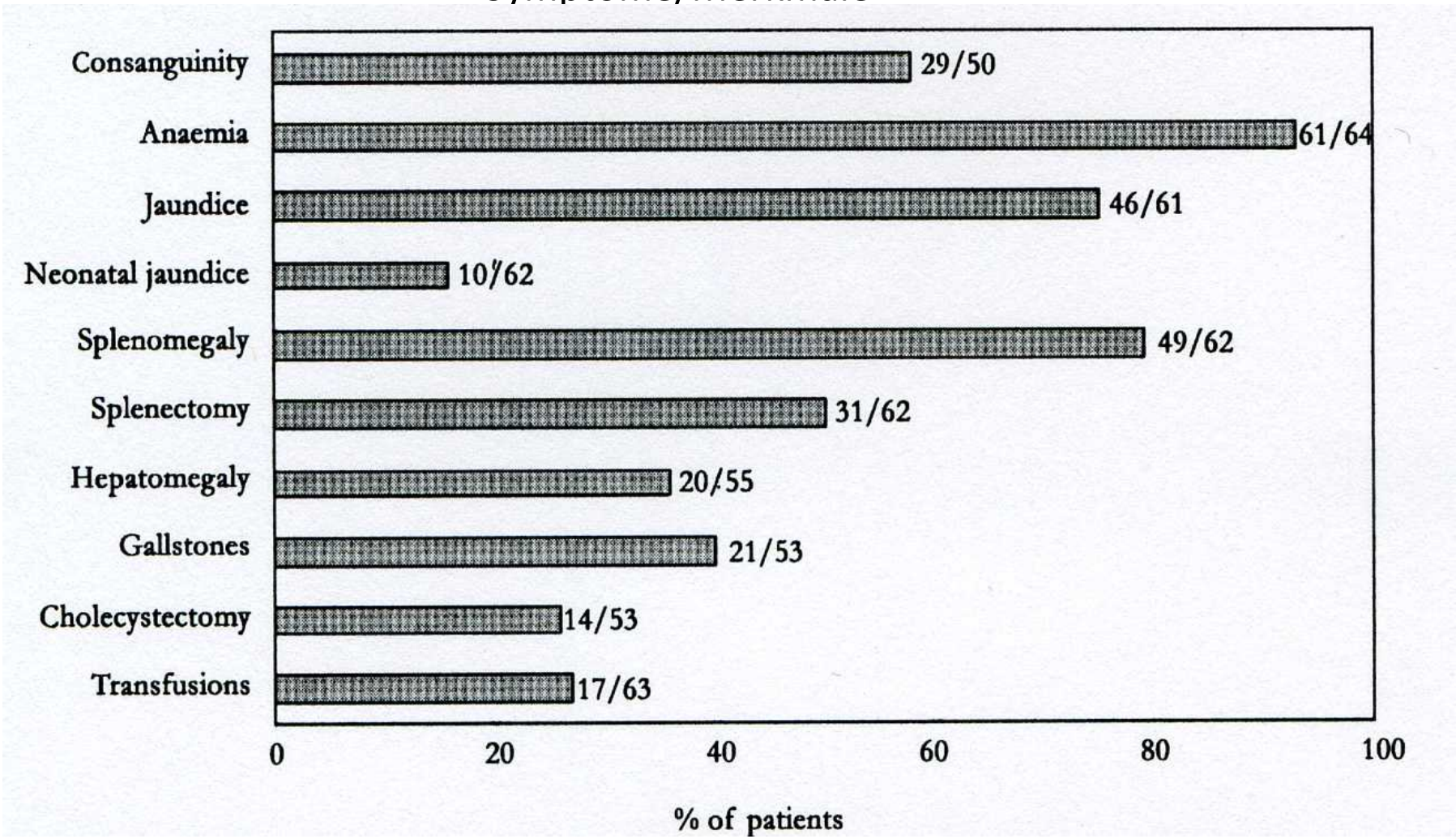
Pyrimidin-Nucleotide: nicht membrangängig

>>Pyrimidin-Nucleotid-Konzentration erhöht

>> Hemmung anderer Enzyme:
Pentosephophatweg,
Ribose-Phosphat-Pyrophosphokinase

>> Hämolyse

Pyrimidin-5`-Nucleotidase-Mangel
- Symptome/Merkmale -



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Pyrimidin-5`-Nucleotidase-Mangel
- Diagnostik -

Blutausstrich mit frischem Blut ohne EDTA-Zusatz: basophile Tüpfelung

UV-Spektroskopie des enteiweißten Cytosols: OD260nm : OD280nm

Blei-Konzentration

Pyrimidin-Nucleotidase-Aktivität

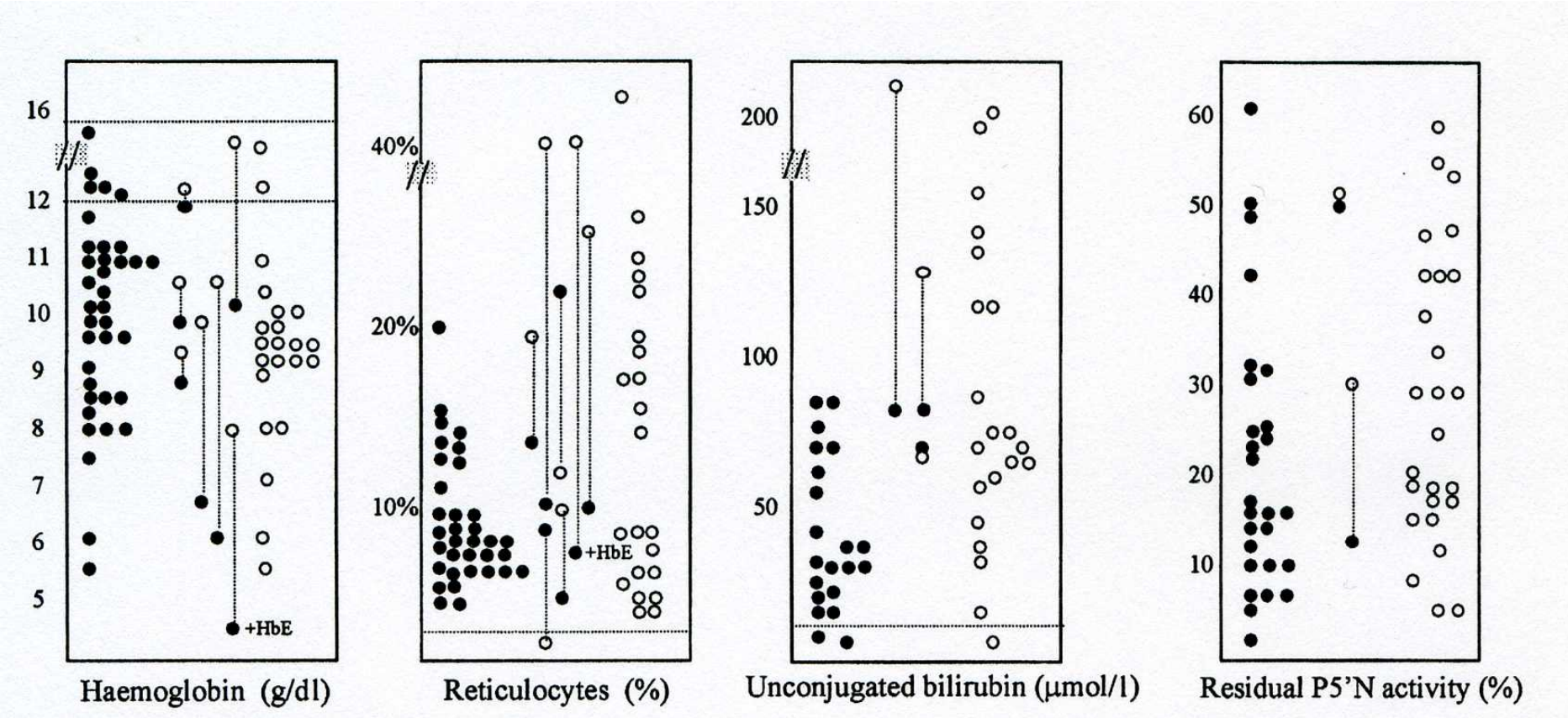
Ribosephosphat-Pyrophosphokinase-Aktivität

Pyrimidin-5`-Nucleotidase-Mangel
- Therapie -

Zumeist nicht erforderlich

Splenektomie: bei schwerem Verlauf,
Besserung der Symptomatik,
Anstieg der Retikulozytenzahl

Pyrimidin-5`-Nucleotidase-Magel
- Splenektomie -



- nicht-splenektomiert
- splenektomiert

Zanella et al. 2006

Pyrimidin-5`-Nucleotidase-Mangel
- eine unterschätzte Erkrankung?

Vermutlich nein,
aber eine leicht zu erkennende Differentialdiagnose
mit therapeutischer Konsequenz