A Reversible Nephrotic Syndrome Associated with Congestive Heart Failure

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Attention is drawn to the occurrence of the nephrotic syndrome during chronic heart failure and to its reversibility over a period of months on a regimen of digitalis, low-salt diet, and weekly, parenterally administered, mercurial diuretics. It is therefore concluded that the nephrotic syndrome was not caused by mercurial diuretics and is not a contraindication to their use. Reference is made to the poorly understood phenomenon of proteinuria in heart failure and its possible relationship to these cases.

A NEPHROTIC syndrome is an unusual and puzzling complication of chronic heart failure about which very little has been written. The object of this communication is to record and to discuss 4 instances in which severe proteinuria, hypoproteinemia, massive edema, hypercholesterolemia, and a strikingly abnormal plasma electrophoretic pattern developed in the course of congestive heart failure and to emphasize the reversibility of the process.

Four similar patients were reported by Munck and Nissen. With the exception of 1 patient who died and came to autopsy, their subsequent courses were not described.

Biochemical Methods

Serum albumin, cholesterol, and urea were estimated according to the method of King and Wootten. Protein concentration in pooled 24-hour urine collections was estimated by the method of Esbach.

Case Reports

Case 1. (H. H., no. 165634). A 50-year-old man was admitted in October 1954 because of paroxysmal and exertional dyspnea and wheezing. Blood pressure was 220/120 mm. Hg, and jugular venous pressure 5 cm. above the sternal angle. There were a soft apical pansystolic murmur, a presystolic triple rhythm, bilateral basal rales, and electrocardiographic evidence of left ventricular hypertrophy. Urinalysis, including microscopic examination of sediment and test for protein, was normal. An intravenous pyelogram was normal, and the kidneys could concentrate urine to a specific gravity of 1.021.

The patient was discharged on digitalis, reserpine, ammonium chloride, and 3 tablets daily of chloromerodrin, an oral mercurial diuretic. In December 1954, he was readmitted for better control of the hypertension. This time the urine had a trace of protein. By means of pentolinium, the blood pressure was satisfactorily lowered to 140/90 mm. Hg recumbent and 115/75 mm. Hg standing. He was given several injections of mersalyl, but because of some skinliness of the skin, it was discontinued. The blood urea was 29 mg. per cent.

In March 1955, the patient was readmitted with a severe acute posterior myocardial infarction with left ventricular failure, and he was given mersalyl by injection, with a good diuresis and weight loss. Nevertheless he began to accumulate saeral edema and by the end of the second hospital week had a proteinuria of 3 to 4 Gm. per day. The urine specific gravity reached 1.025 after 24 hours' dehydration, and the urea clearance was normal. Seventy per cent of an injected test dose of Congo red was still in the blood after 1 hour. The infarction evolved in the usual way, and he continued to receive a weekly 2-ml. injection of mersalyl. At the time of discharge in April 1955, there was some ankle edema, the total serum protein was 6.2 Gm. per cent, and there was a proteinuria of 3 to 4 Gm. per 24 hours. Digoxin and weekly mersalyl were continued on an out-patient basis. He felt well, but in February 1956 was readmitted because the edema and proteinuria persisted. The blood pressure was 190/100 mm. Hg and there were rales at the lung bases as well as massive dependent edema. The urine showed a few hyaline casts and contained 9 Gm. of protein per 24 hours. No organisms grew from a urine culture. The blood urea was 37 mg. per cent. The blood cho-
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lesterol was now 377 mg. per cent, and the total serum protein 5.5 Gm. per cent with 1.3 Gm. per cent albumin. Another Congo red test was normal. Renal biopsy showed "a patchy thickening of the capillary basement membranes," a finding that is not uncommon in congestive heart failure. Retrograde inferior caval venography showed no inferior vena caval or renal vein obstruction. The urea clearance was 100 per cent of normal. Cortisone was without effect on the proteinuria. Throughout his stay he received periodic mersalyl injections, and when he was discharged in April 1956, he had begun to have a small diuresis with each of them. From this time he has been seen in the out-patient department, where, in March 1957, he was feeling well and was without edema of the ankles. He was still taking a weekly injection of mersalyl in addition to digoxin, ammonium chloride, and a low-salt diet. Mecamylamine was substituted for pentolinium. His blood pressure was 150/90 mm. Hg, blood urea 42 mg. per cent, blood electrolytes all normal, cholesterol 220 mg. per cent, and serum albumin 2.4 Gm. per cent. The albumin/globulin ratio was still reversed, however, and a qualitative sulfosalicylic acid test for urine protein revealed a heavy cloud. He has been back at regular work for 1 year (figs. 1 and 2).

Case 2. (H. H., no. 161211). A 43-year-old woman, with symptomatic mitral valve disease and atrial fibrillation for 13 years, had, for the last 3 years of her life, evident tricuspid incompetence with a pulsating liver and mild jaundice. From April 1954, at which time her urine was free of protein, she received either a weekly 2-ml. injection of mersalyl or 2 daily tablets of an oral mercurial diuretic (chloromerodrin) in addition to digitalis and a low-salt diet. In November 1955, she was free of edema and doing well, but in January 1956 her dyspnea and ankle edema increased. In May 1956, she was admitted to the hospital with grossly edematous legs and sacrum and bilateral basal rales. The jugular venous pressure was 10 cm. above the sternal angle, with a pronounced systolic pulsation. Urine protein excretion varied from 3 to 10 Gm. a day. No organisms grew from urine culture. The total

Fig. 1. Progress chart of case 1. *Results of qualitative test (sulfosalicylic acid) on single-voided specimens and estimated level of 24-hour excretion. †Times corresponding to electrophoretic patterns in figure 2. Dotted lines, normal level (approximately).
serum proteins were 5.5 Gm, per cent with albumin 2.2 Gm. per cent. Serum cholesterol was 683 mg. per cent. Serum electrolytes and blood urea were normal. Eighty-two per cent of an injected test dose of Congo red was still in the plasma after 1 hour. An intravenous pyelogram was normal. Mercurial administration was discontinued and 8 weeks later there were 395 μg. of mercury in a 24-hour collection of urine. A course of dimer- caprol was administered, and 7 days later there were still 315 μg. of mercury in the urine per 24 hours. Edema continued to accumulate, and therefore, on the basis of experience with case 1, mercurial injections were given again. This time she was given mercaptomerin in 2-ml. weekly, subcutaneous injections, and after each injection she had a small diuresis. Edema began to lessen, and by August 1956, the urine contained only 2 Gm. protein per 24 hours. She was therefore discharged from the hospital and remained at home as a semi-invalid (her exercise tolerance being severely restricted), receiving maintenance digitalis, a low-salt diet, ammonium and potassium chloride supplements, and twice weekly injections of mercaptomerin. In January 1957, there was only a moderate degree of pretibial edema and a faint trace of urinary protein by qualitative test. In March 1957 edema had disappeared, and many repeated qualitative tests for urine protein were negative. She continued to receive mercaptomerin up to and during her last admission to the hospital in March 1957, when her cardiac status suddenly deteriorated and she died. At postmortem examination, organic disease of the mitral valve was found with predominant incompetence and functional dilatation of the tricuspid valve ring without evident organic involvement. There was no evidence of old or recent thrombus in renal or inferior vena caval vessels, and histologic examination of the kidneys revealed only some protein material in a few tubules (figs. 3 and 4).

**Case 3.** (H. H., no. 189473). A 53-year-old woman had proteinuria, ankle edema, and hypertension with her last 2 pregnancies at the ages of 33 and 37, respectively, and was known to be hypertensive thereafter. At age 49 her blood pressure was 240/150 mm. Hg, and because of some dyspnea and ankle edema, she was given digitalis and 1 or 2 injections of mersalyl. Her blood urea was 39 mg. per cent. At age 50, because of recurrence of dyspnea and edema and blurring of vision, she was treated with hexamethonium and weekly injections of mersalyl, and for 2 years her symptoms and signs remained minimal. At age 52 dyspnea and edema returned, and she was admitted to her local hospital. Blood pressure was 220/130 mm. Hg, and pentolinium and reserpine were substituted for hexamethonium. The blood pressure fell to 140/80 mm. Hg, but at the same time edema continued to accumulate, and it was found that the pressure stayed at 140/80 mm. Hg even when pentolinium and reserpine were stopped. Mercurial injections now had no diuretic effect. Gross proteinuria developed, but the blood urea remained at 22 mg. per cent. She was discharged from the hospital because she felt well in spite of the extensive edema, and, while at home, she continued to receive weekly mersalyl injections and digitalis. Nevertheless, the edema increased and began to involve her thighs, and she was therefore readmitted to her local hospital. The blood pressure was 130/85 mm. Hg, blood urea 20 mg. per cent, serum albumin 2.4 Gm. per cent, and globulin 5.5 Gm. per cent. Cholesterol was 450 mg. per cent. A diagnosis of “mercurial nephrosis” was made and mersalyl was discontinued. With Southey tubes 58 pints of edema fluid were removed over an 8-month period in the hospital, during which infusions of Dextran and courses of dimercaprol, corticotropin, and cortisone were without effect. The blood urea was
always within normal limits except on 1 occasion when it was 67 mg. per cent.

In August 1956, at a time when even her hands and face were becoming puffy, she was transferred to Hammersmith Hospital. On admission blood pressure was 210/120 mm. Hg and there was controlled atrial fibrillation. The left ventricle was enlarged, and there was a third sound at the apex. Jugular venous pressure was 10 cm. above the sternal angle with a systolic pulsation indicating tricuspid incompetence. Twenty-four-hour urine collections contained 9 Gm. protein, the blood cholesterol was 600 mg. per cent, serum albumin 1.1 Gm. per cent, and globulin 2.9 Gm. per cent. Daily urine volumes averaged 1500 ml., serum electrolytes were normal, urinary sediment was normal, and urine cultures were sterile. An insignificant amount of mercury was excreted per 24 hours (70 µg.). A Congo red test gave a negative result. Regular, twice weekly, intramuscular injections of mersalyl were started in the second week, and although at first without effect, it was found that when intravenous aminophylline was given at the same time, satisfactory diureses of 2,000 to 4,000 ml. resulted. On this form of treatment and with a diet containing 200 mg. of sodium and 200 Gm. of protein daily, her condition steadily improved. Edema lessened, and weight fell from 79.1 Kg. shortly after admission to 63.6 Kg. when she was discharged nearly 3 months later. Toward the latter part of her stay, mersalyl alone, without aminophylline, was again causing satisfactory diuresis. Weekly mersalyl injections, digitalis, and low-salt diet with high-protein supplements were therefore continued at home, and 4 months later in March 1957, when she was readmitted to Hammersmith Hospital for re-evaluation, edema was absent, the urine contained only 2 Gm. protein per 24 hours, and the blood cholesterol had fallen to 265 mg. per cent. The serum albumin was still only 1.7 Gm. per cent. Globulin was 3.4 Gm. per cent. Electrolytes were all normal. Chromatography of the urine revealed no abnormal aminoaciduria. By May 1957, the blood cholesterol was 242 mg. per cent, and the serum albumin 3.3 Gm. per cent, with globulin 2.5 Gm. per cent. A retrograde inferior vena caval angiogram showed no obstruction of the inferior vena cava or of the renal veins. She felt well and had only moderate dyspnea on exertion (figs. 5 and 6).
consistently been significant. The urine protein content varied from 1 to 6.9 Gm. per 24 hours, and the total serum proteins were 5.1 Gm. per cent (albumin 1.4, globulin 3.7). The serum cholesterol was 280 mg. per cent, and the blood urea 24 mg. per cent. She died suddenly in mid-October 1957, and at autopsy a large atrial septal defect was found. The pulmonary arteries were enormously dilated. The kidneys appeared congested but were otherwise normal, and microscopic examination revealed no definite abnormality. There was no evidence of a renal vein thrombosis.

**DISCUSSION**

**Differential Diagnosis**

The nephrotic syndrome may appear during the course of any of several disease conditions, most of which can be reasonably shown not to have been present in these 4 patients.

In adults the nephrotic syndrome may arise during the course of a primary renal disorder, but there is good reason to believe that none of these patients was suffering from pre-existing renal disease, because there was no azotemia, and cells were absent from the urine of all. In case 1, furthermore, renal biopsy failed to reveal any evidence of nephritis, and in cases 2 and 4 the kidneys were grossly and microscopically normal after death.

Secondary renal amyloid deposits are sometimes associated with the nephrotic syndrome, but in no instance was there a primary disease of the kind usually associated with secondary amyloidosis, and Congo red tests were negative. In cases 1, 2, and 4 no amyloid material was found in the kidneys.

We could find no evidence in any of our patients of “collagen” disease, another of the conditions known to be associated with the nephrotic syndrome. None was febrile, in case 1 a search for LE cells was negative, and in cases 2 and 4 “collagen” disease was excluded by the autopsy findings.

No evidence of recanalized thrombosis of the inferior vena cava or renal veins was found in the patients who came to autopsy, and retrograde venography eliminated any significant renal venous or caval block in the other 2.6

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**Case 4.** (H.H., no. 185083). A 70-year-old woman with an atrial septal defect had been receiving digitalis for heart failure since 1952. From late 1955 until January 1957, she had been receiving almost weekly parenteral mercurial diuretics. These were discontinued in January 1957 because of development of the nephrotic syndrome. In June 1957, she was passing up to 9 Gm. of protein in the urine each day, and the serum albumin was 2.1 Gm. per cent. The serum electrolytes remained normal, except for a slight but consistently elevated serum bicarbonate, and the blood urea never rose above 45 mg. per cent. The serum cholesterol rose from 212 mg. per cent in January 1957 to 357 mg. per cent in June 1957. No significant pyuria or microscopic hematuria had ever been evident.

After the mercurial diuretics were discontinued, the patient was treated with ion-exchange resins and a low-salt diet (1 Gm. of sodium chloride daily). Some improvement occurred, but she was readmitted to the hospital in September 1957 with extensive edema and jugular venous pressure 5 cm. above the sternal angle. Mercurial diuretics were now administered, but were without effect upon either the heart failure or nephrotic syndrome. The urine protein content varied from 1 to 6.9 Gm. per 24 hours, and the total serum proteins were 5.1 Gm. per cent (albumin 1.4, globulin 3.7). The serum cholesterol was 280 mg. per cent, and the blood urea 24 mg. per cent. She died suddenly in mid-October 1957, and at autopsy a large atrial septal defect was found. The pulmonary arteries were enormously dilated. The kidneys appeared congested but were otherwise normal, and microscopic examination revealed no definite abnormality. There was no evidence of a renal vein thrombosis.

**Fig. 4. Electrophoretic patterns of plasma proteins in case 2. a. An essentially normal pattern in 1954. b. At the height of the nephrotic syndrome in 1956. c. The improved pattern of March 1957.**
None of the cases was diabetic, and therefore Kimmelstiel-Wilson’s intercapillary glomerulosclerosis does not enter into the differential diagnosis.

The Possible Role of Mercurial Toxicity

It may be asked whether the mercurial diuretics administered to these patients therapeutically could have had an adverse effect on kidney function.

Munck and Nissem,\(^1\) who described 4 cases of nephrotic syndrome complicating heart failure, incriminated mercurial diuretics, although the kidneys of their patient who was autopsied (death from pulmonary embolus) showed “no definite changes” either grossly or microscopically. What is more, the authors were apparently unaware of the potential reversibility of the clinical picture, even in the face of continued mercurial diuretic administration.

Certain alleged instances of “toxic nephrosis” from mercurial diuretics\(^7,8\) seem in retrospect to have been instances of “low-salt syndrome” with a great deal of edema, and another in a patient who had received an oral mercurial diuretic lacks detailed documentation.\(^9\)

Although we are inclined to doubt that any etiologic role was played by the mercurial diuretics used for therapy, there are some strong traditional arguments in favor of a mercurial etiology: 1. Proteinuria has been known for years to occur in patients repeatedly exposed to small quantities of metallic mercury in the treatment of syphilis.\(^10\) 2. Factory workers exposed to the mercury salt of fulminic acid sometimes develop the clinical picture of nephrosis.\(^11\) 3. Children exposed to calomel-santonin vermifuge\(^10\) and calomel-containing teething powders\(^12\) are reported to have developed nephrosis.
Batterman and co-workers\textsuperscript{16} reported that in 4 patients who received oral mercurial therapy there was "increasing proteinuria" and "fear of impending generalized mercurialism prompted the cessation of therapy." However, these patients later returned to the hospital in such severe congestive failure that administration of the oral diuretic was re-instituted in spite of the proteinuria. All had a favorable diuretic response and showed "no further evidence of toxicity." This experience is reminiscent of our own.

Kaplan and co-workers\textsuperscript{17} found that 5 of 15 patients treated with oral mercurial preparations had proteinuria, but "it could not be attributed to the oral mercurial." No reasons are given to substantiate this opinion, however. Griffith and co-workers\textsuperscript{18} followed 12 patients in heart failure for 8 to 65 months while they were treated with the orally administered chloromerodrin, and in no instance did proteinuria occur where it had been absent before the onset of therapy.

We wish to emphasize that in the 3 of our cases that were studied most closely, the nephrotic syndrome disappeared, even though they continued to receive mercurial diuretics. In view of this we do not believe that these patients were at any time suffering kidney damage from mercurial toxicity. Case 4 was not studied as fully as were the first 3 cases, and it is not possible properly to assess the effect of mercurial diuretics in this instance. However, this patient is of interest as another example of the occurrence of nephrotic syndrome without obvious cause in a patient with congestive heart failure.

\textbf{The Association of Proteinuria and Nephrotic Syndrome with Congestive Heart Failure}

It seems preferable to look for the cause of the nephrotic syndrome in the disturbed physiology of heart failure itself. Proteinuria, to be sure, is the rule in congestive failure, and we suggest that in rare instances this proteinuria may be gross enough and prolonged enough to give rise to the nephrotic syndrome.\textsuperscript{4, 5} Race and co-workers\textsuperscript{19} studied 161 cases of congestive heart failure that came

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig6.png}
\caption{Electrophoretic patterns of plasma proteins in case 3. a, and b. Patterns during height of the nephrotic syndrome. c, Pattern about 9 months later when nephrotic syndrome had subsided.}
\end{figure}

On the other hand, we are not aware of any unequivocal evidence that mercurial diuretics employed in the usual therapeutic dosage are able to produce the nephrotic syndrome. Indeed, a controlled study by Coblentz and co-workers\textsuperscript{13} demonstrates that parenteral administration of mercurial diuretics in heart failure causes neither a rise in blood nonprotein nitrogen nor an increase in proteinuria, even when azotemia and significant proteinuria are present at the onset of treatment.

Still, it is pertinent to ask whether orally administered mercurials are peculiarly likely to cause proteinuria, because it is established that mercury given in this fashion enjoys a significantly delayed excretion and more accumulation within the body than when it is given parenterally.\textsuperscript{14, 15} Two of our patients received an oral mercurial at some time before the onset of the nephrotic syndrome, and 1 of Munck and Nissen's cases received an oral mercurial exclusively.
to autopsy; and of these, 142 were known to have had proteinuria, although in none was there histologic evidence of a significant renal lesion. There was, however, a good correlation between the amount of proteinuria and the clinical severity of congestive heart failure, and in 1 case where the proteinuria and degree of failure had been gross, the kidneys were histologically normal. Our own experience is in agreement with these observations.

We can only speculate on how the proteinuria of congestive failure comes about. In general, proteinuria is thought to be associated with increased glomerular filtration of protein, but the part played by tubular dysfunction is uncertain. Current concept holds that minimal glomerular filtration and subsequent tubular reabsorption of protein occur in the normal kidney, and the degree of proteinuria in our cases could be explained by tubular inability to reabsorb the normally filtered protein. However, the absence of serum electrolyte abnormalities or abnormal aminoaciduria (case 3) argue somewhat against tubular abnormality. The situation is complicated by observations that show that globulin as well as albumin is lost by the kidney in congestive heart failure, and the urinary concentration of globulin is alleged to bear no relation to its level in the serum.

Węgria and co-workers have shown in animals that renal congestion causes proteinuria. Proteinuria and nephrotic syndrome occur in man when there is renal vein or inferior vena caval occlusion and has complicated chronic constrictive pericarditis where it has been relieved by pericardiectomy. The detailed chain of events that links venous congestion with proteinuria remains obscure, however. In our cases of nephrotic syndrome there was no impressive correlation between the height of the venous pressure and the degree of proteinuria. Nor have we found the duration of a raised venous pressure to be closely related, for we have seen many patients with prolonged and severe congestive heart failure and tricuspid incompetence who have not developed a nephrotic syndrome.

Whatever the cause of the nephrotic syndrome in these patients, the evidence suggests that mercurial diuretics are not implicated and that the syndrome may be the result of the heart failure itself. In such cases, provided there is no clear evidence of mercurial toxicity, such as a rash, abdominal pain, gingivitis, or evidence of acute renal damage with a suddenly rising blood urea, and provided that a satisfactory diuresis can be produced, mercurial diuretics should not be withheld. Indeed, we suggest that they are definitely indicated. Massive edema and proteinuria in the presence of a normal blood urea and a normal urinary sediment do not by themselves contraindicate their use.

Summary
Attention is drawn to 4 instances of the nephrotic syndrome occurring during the course of chronic heart failure. All developed gross proteinuria, massive edema, hypalbuminemia, strikingly abnormal plasma electrophoretic patterns, and hypercholesterolemia with a normal or only slightly elevated blood urea and with a normal urinary sediment. Recovery from the nephrotic syndrome occurred in 3 patients over a period of 9 months on a regimen of digitalis, low-salt and high-protein diet, and regular, weekly, intramuscular administration of mercurial diuretics. Aminophylline given intravenously just prior to the mercurial was found to enhance the diuretic response.

Reference is made to the little understood but common phenomenon of proteinuria in heart failure. The possible relationship of the proteinuria to the occasional case of nephrotic syndrome is discussed.

It is concluded that the nephrotic syndrome occurring in chronic heart failure is not caused by mercurial diuretics and is not in itself a contraindication to their continued use.

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SUMMARIO IN INTERLINGUA

Es presentate 4 casos de syndrome nephrotic, occurrente durante le curso de chronic insufficientia cardiaca. Omnes monstrava le disveloppamento de grossier proteinuria, edema massive, hypoalbuminemia, frappante anormalitates del configuration electrophoretic del plasma, e hypercholesterolemia, con normal o levemente elevate niveles de urea del sanguine e normal sedimentation urinari. In tres del patientes, restablimento ab le syndrome nephrotic occurreva in le curso de un periodo de 9 menses de un regime de digitalis, dieta a basse contento de sal e a alte contento de proteina, e regular administrationes septimanal de diuretics mercurial per via intra-muscular. Esseva constatate que le administration de aminophyllina per via intravenose justo ante le administration del diuretic mercurial resultava in un melioration del effecto.

Es signalate le paucem comprehendite sed commun phenomeno de proteinuria in insufficientia cardiaca. Es discutite le relation possibile inter le proteinuria e le sporadic occurrentia de syndrome nephrotic.

Es conclusite que le syndrome nephrotic occurrente in chronic insufficientia cardiaca non es causate per diuretics mercurial e non representa per se un indication contra le continuation de lor uso.

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REVERSIBLE NEPHROTIC SYNDROME


Medical Eponyms

By Robert W. Buck, M.D.

Hanot's Cirrhosis. Victor Charles Hanot (1844-1896) presented "A Study of a Type of Hypertrophic Cirrhosis of the Liver (Hypertrophic Cirrhosis with Chronic Jaundice)" (Étude sur une forme de Cirrhose hypertrophique du foie (Cirrhose hypertrophique avec icterus chronique) to the Paris Faculty of Medicine as his thesis for the doctorate. This is Thesis No. 465 of the Faculty of Medicine of Paris, and was published in 1875. The following quotation is taken from page 89.

"Among the various lesions of the liver which have been included under the name of hypertrophic cirrhosis, there is one which is distinguished by the following features: intralobar sclerosis, abnormal development and chronic catarrh of the smaller bile ducts.

"The clinical form is no less characteristic: It is an affection which first shows itself by chronic jaundice, due to obliteration of the smaller bile ducts, and by a considerable hypertrophy of the liver without ascites or abnormal enlargement of the subcutaneous abdominal veins such as is seen in classic cirrhosis.

"Usually this disease follows a prolonged course, and may continue for several years without any marked alteration in the state of nutrition. It also usually terminates in the syndrome known as icterus gravis.

"By reason of all these peculiarities, it would seem to deserve a separate place in the nosological category. One might term it hypertrophic sclerosis of the liver with chronic jaundice."
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