Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura

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The Birth of the Hemolytic Uremic Syndrome

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CLINICAL ASPECTS

Conrad Gasser (Fig. 1) obtained his M.D. degree in 1937 and then trained in microbiology, morbid anatomy, and internal medicine. In 1941 he became a resident at the Zurich Kinderspital under the prestigious leadership of Guido Fanconi. From 1945–1956, Gasser was Oberarzt (chief resident). Besides a heavy load of clinical responsibilities and teaching, he pursued intensive research activities in hematology. Gasser described a form of anemia in premature babies with spontaneous formation of Heinz bodies (1948) and acute erythroblastopenia (1949). His monograph *Die Hämolytischen Syndrome des Kindesalters* was published in 1951. It contained a wealth of carefully documented observations which earned him his venia legendi and established his international reputation. As Oberarzt, Conrad Gasser was the tutor of the incoming residents who worked initially in a large ward called Saal 4. He was an astute, original clinician with vast experience. He guided residents through their clinical apprenticeship and in the absorbing and fascinating field of hematology wherein they did all the blood counts and examined blood smears and bone marrow aspirates.

Emile Gautier entered the Kinderspital of Zurich in the fall of 1952, after 2 years in physiology in Bern with Alexandre von Muralt, 2 years as research fellow with Alan Butler of the Massachusetts General Hospital, and one year of internal medicine in Geneva. While in Boston, he had been exposed to John Merrill's work on acute renal insufficiency.

The first patient described in the original paper of 1955 was seen in May 1953. Cases 4, 2, and 3 were admitted in January, February, and July 1954. A retrospective search identified case 5, who was seen in 1952. All patients died. Gautier remembers admitting cases 1 and 2. The medical records of four of those five patients were retrieved from the files of the Kinderspital in 1989. Figure 2 shows the upper part of

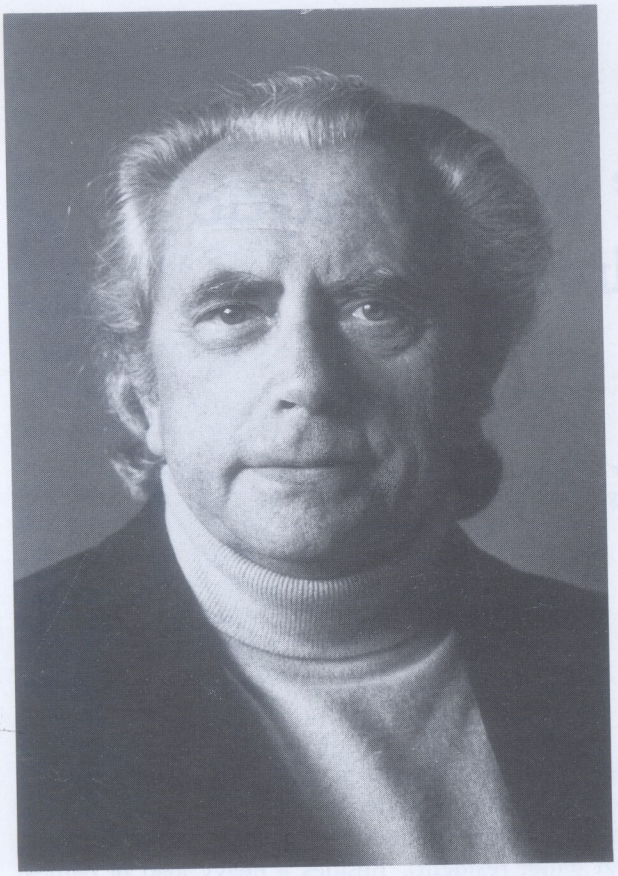
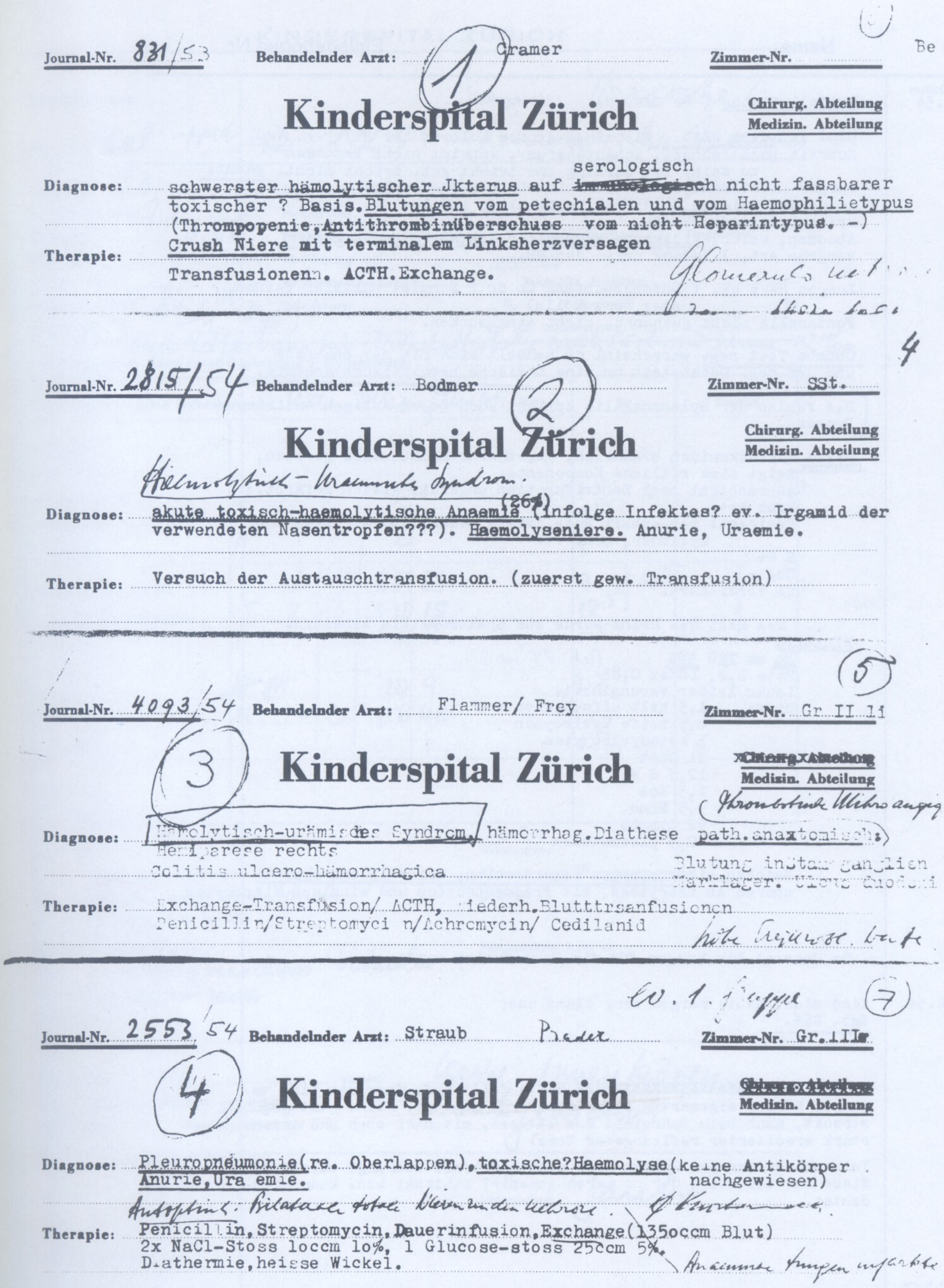


Figure 1 Professor Conrad Gasser, 1912–1982.

the front page of these records. The diagnoses are descriptive, and the numerous question marks attest to the perplexity of the house staff. The handwritten annotations were added by Conrad Gasser as the results of the postmortem examination became available. The diagnosis "hemolytic uremic syndrome" was made on clinical grounds in patient 3.

Figure 3 shows the transcription, carried out by Gasser, of the emergency status of case 2; Figures 4 and 5 show the evaluation of her blood and bone marrow aspirate on admission. It was also possible to look back to the slides of the peripheral blood and bone marrow aspirates of all patients. Mrs. S. Adank-Stahel, laboratory technician at the Kinderspital at the time the patients were observed, kindly reviewed each slide this year. She confirmed that megacaryocytes are present in the bone marrow, sometimes in increased and sometimes in decreased numbers. Platelet-forming megacaryocytes are either decreased or absent. Figure 6 shows the bone marrow smear of patient 1. She saw schizocytes in every blood smear, although this finding was not mentioned in the original paper in regard to patient 1.

The Pathology Institute is situated in the Kantonsspital area at a distance from the Kinderspital. Every week Guido Fanconi and his Oberärzte and residents paced rapidly along the Freiestrasse to attend the clinicopathological confrontations. Cases



Journal-Nr. 831/53 Behandelnder Arzt: Cramer Zimmer-Nr.

(1)

Kinderspital Zürich

Chirurg. Abteilung
Medizin. Abteilung

Diagnose: schwerster hämolytischer Jkterus auf ~~immunologisch~~ serologisch nicht fassbarer toxischer ? Basis. Blutungen vom petechialen und vom Haemophilietypus (Thrompopenie, Antithrombinüberschuss vom nicht Heparintypus. -) Crush Niere mit terminalem Linksherzversagen

Therapie: Transfusionenn. ACTH. Exchange.

Journal-Nr. 2815/54 Behandelnder Arzt: Bodmer Zimmer-Nr. SSt.

(2)

Kinderspital Zürich

Chirurg. Abteilung
Medizin. Abteilung

Diagnose: akute toxisch-haemolytische Anaemie (26.) (infolge Infektes? ev. Irgamid der verwendeten Nasentropfen???). Haemolyseniere. Anurie, Uraemie.

Therapie: Versuch der Austauschtransfusion. (zuerst gew. Transfusion)

Journal-Nr. 4093/54 Behandelnder Arzt: Flammer/ Frey Zimmer-Nr. Gr II li

(3)

Kinderspital Zürich

~~Chirurg. Abteilung~~
Medizin. Abteilung

Diagnose: Hämolytisch-urämisches Syndrom, hämorrhag. Diathese path. anatomisch:
Hemiparese rechts Blutung in Stammganglien
Colitis ulcero-hämorrhagica Marklager. Ulcus duodeni

Therapie: Exchange-Transfusion/ ACTH, wiederh. Bluttransfusionen
Penicillin/Streptomycin/Achromycin/ Cedilanid

Journal-Nr. 2553/54 Behandelnder Arzt: Straub Zimmer-Nr. Gr. III

(4)

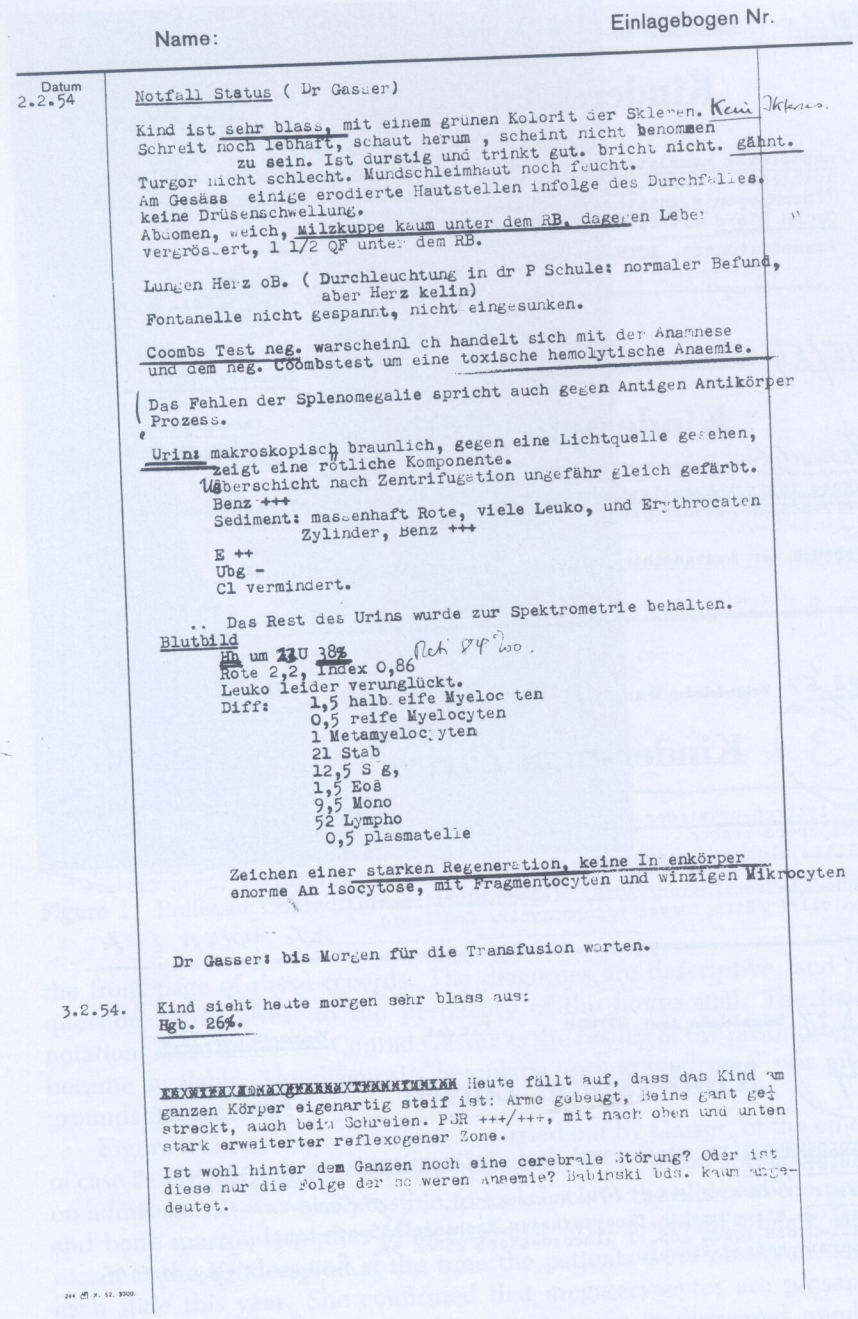
Kinderspital Zürich

~~Chirurg. Abteilung~~
Medizin. Abteilung

Diagnose: Pleuropnéumonie(re. Oberlappen), toxische? Haemolyse (keine Antikörper nachgewiesen)
Anurie, Ura emie.

Therapie: Penicillin, Streptomycin, Dauerinfusion, Exchange(1350ccm Blut)
2x NaCl-Stoss 10ccm 10%, 1 Glucose-stoss 250ccm 5%.
Diathermie, heisse Wickel.

Figure 2 Front pages of the medical records of four patients admitted to the Kinderspital of Zurich.



Name: Einlagebogen Nr.

Datum 2.2.54

Notfall Status (Dr Gasser)

Kind ist sehr blass, mit einem grünen Kolorit der Sklerren. Kein Ikterus.
Schreit noch lebhaft, schaut herum , scheint nicht benommen zu sein. Ist durstig und trinkt gut. bricht nicht. gähnt.
Turgor nicht schlecht. Mundschleimhaut noch feucht.
Am Gesäss einige erodierte Hautstellen infolge des Durchfalles.
keine Drüsenschwellung.
Abdomen, weich, Milzkuppe kaum unter dem RB, dagegen Leber vergrössert, 1 1/2 QF unter dem RB.

Lungen Herz oB. (Durchleuchtung in dr P Schule: normaler Befund, aber Herz kelin)
Fontanelle nicht gespannt, nicht eingesunken.

Coombs Test neg. warscheinl ch handelt sich mit der Anamnese und dem neg. Coombstest um eine toxische hemolytische Anaemie.

Das Fehlen der Splenomegalie spricht auch gegen Antigen Antikörper Prozess.

Urin: makroskopisch braunlich, gegen eine Lichtquelle gesehen, zeigt eine rötliche Komponente.
Überschicht nach Zentrifugation ungefähr gleich gefärbt.
Benz +++
Sediment: massenhaft Rote, viele Leuko, und Erythrocaten Zylinder, Benz +++
E ++
Ubg -
Cl vermindert.

.. Das Rest des Urins wurde zur Spektrometrie behalten.

Blutbild
Hb um 11 U 38% Ret 84‰.
Rote 2,2, Index 0,86
Leuko leider verunglückt.
Diff: 1,5 halb eife Myeloc ten
0,5 reife Myelocyten
1 Metamyelocyten
21 Stab
12,5 S g,
1,5 Eos
9,5 Mono
52 Lympho
0,5 plasmatelle

Zeichen einer starken Regeneration, keine Immunkörper
enorme An isocytose, mit Fragmentocyten und winzigen Mikrocyten

Dr Gasser: bis Morgen für die Transfusion warten.

3.2.54. Kind sieht heute morgen sehr blass aus:
Hgb. 26%.

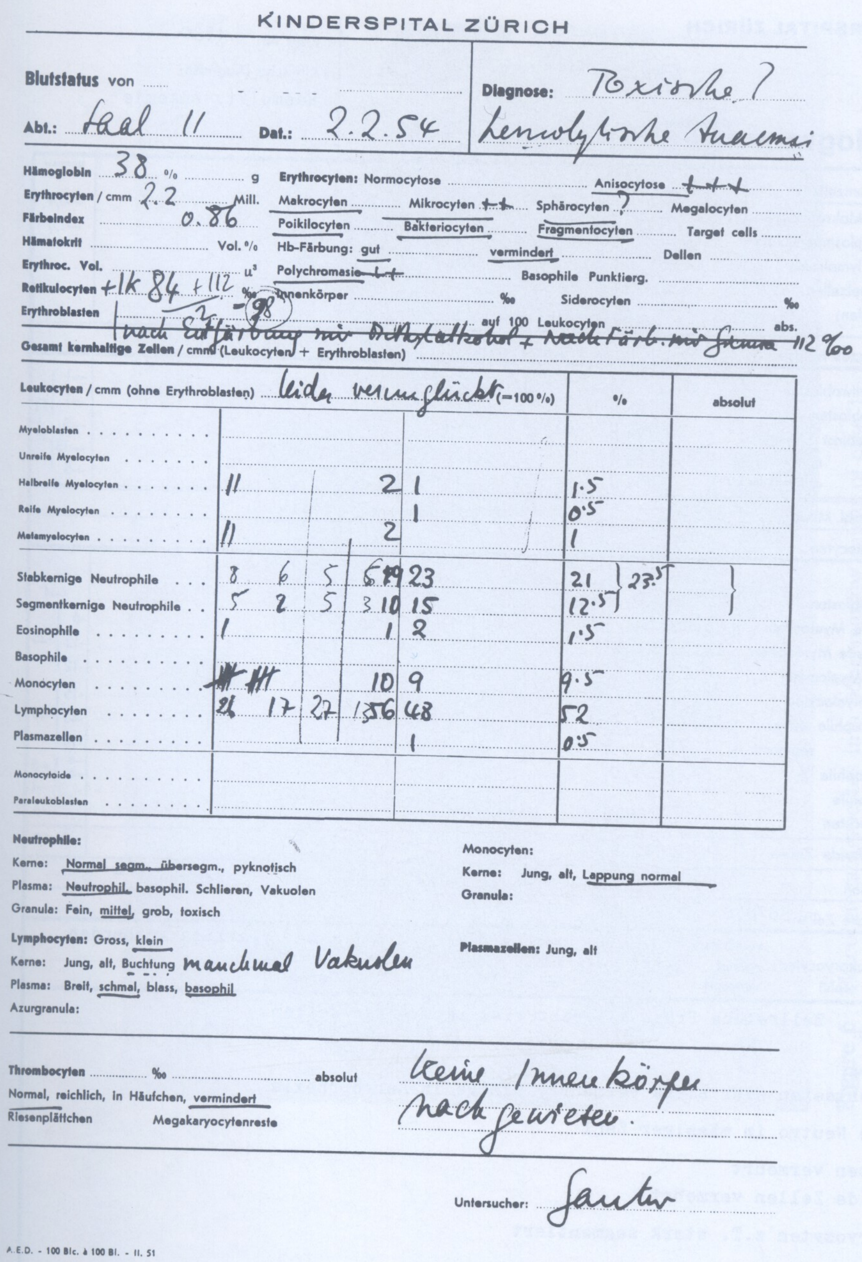
Heute fällt auf, dass das Kind am ganzen Körper eigenartig steif ist: Arme gebeugt, Beine ganz gestreckt, auch beim Schreien. PSR +++/+++, mit nach oben und unten stark erweiterter reflexogener Zone.

Ist wohl hinter dem Ganzen noch eine cerebrale Störung? Oder ist diese nur die Folge der schweren Anaemie? Babinski bds. kaum angedeutet.

244 VI. 52. 3000

Figure 3 Emergency physical examination of case 2 by Dr. Gasser.

were reviewed and the pertinent slides were available for microscopic examination. At one of those confrontations, they learned that case 1 did not present with a shock-kidney but a glomerulonephritis necroticans acuta, which could be viewed as a minimal form of cortical necrosis. Case 2 was discussed with the pathologist in May



KINDERSPITAL ZÜRICH
Blutstatus von
Diagnose: Toxische ?
Abt.: Saal 11 Dat.: 2.2.54 hemolytische Anaemie
Hämoglobin 38 %
Erythrocyten / cmm 2.2 Mill.
Färbeindex 0.86
Hämatokrit Vol. %
Erythroc. Vol. u³
Retikulocyten +lk 84 + 112 ‰
Erythroblasten
Gesamt kernhaltige Zellen / cmm (Leukocyten + Erythroblasten)
Erythrocyten: Normocytose Anisocytose +++
Makrocyten Mikrocyten ++ Sphärocyten ? Megalocyten
Poikilocyten Bakteriocyten Fragmentocyten Target cells
Hb-Färbung: gut vermindert Dellen
Polychromasie ++ Basophile Punktierg.
Innenkörper ‰ Siderocyten ‰
auf 100 Leukocyten abs.
nach Entfärbung mit Methylalkohol + Nachfärb. mit Giemsa 112 ‰
Leukocyten / cmm (ohne Erythroblasten) leider verunglückt (=100 %) % absolut
Myeloblasten
Unreife Myelocyten
Halbreife Myelocyten 1 2 1 1.5
Reife Myelocyten 1 0.5
Metamyelocyten 1 2 1
Stabkernige Neutrophile 8 6 5 6 23 21 23.5
Segmentkernige Neutrophile 5 2 5 3 10 15 12.5
Eosinophile 1 1 2 1.5
Basophile
Monocyten 10 9 9.5
Lymphocyten 26 17 27 56 48 52
Plasmazellen 1 0.5
Monocytoide
Paraleukoblasten
Neutrophile:
Kerne: Normal segm., übersegm., pyknotisch
Plasma: Neutrophil, basophil. Schlieren, Vakuolen
Granula: Fein, mittel, grob, toxisch
Lymphocyten: Gross, klein
Kerne: Jung, alt, Buchtung manchmal Vakuolen
Plasma: Breit, schmal, blass, basophil
Azurgranula:
Monocyten:
Kerne: Jung, alt, Lappung normal
Granula:
Plasmazellen: Jung, alt
Thrombocyten ‰ absolut
Normal, reichlich, in Häufchen, vermindert
Riesenplättchen Megakaryocytenreste
keine Innenkörper nach gewiesen.
Untersucher: Gautier
A.E.D. - 100 Blc. à 100 Bl. - II. 51

Figure 4 Peripheral blood examination of case 2 on admission.

54, case 4 in June 54. The medical record of case 5 could not be retrieved, but his hemolytic anemia and anuria had occurred in the presence of a pneumonitis with pleural empyema. The Coombs' test was positive and, during the cross-matching, a polyagglutination had been noted.

By early May 1955, graphs were drawn in the typical style of Fanconi's Kinder-

KINDERSPITAL ZÜRICH

Name: 7 Wo. Abt.: S.St. Präp. Nr. 4590

Klinische Diagnose: Haemolyt. Anaemie

Myelogramm ~~Sternum~~ Tibia ~~Becken~~

Dat.: 3. II. 54.

				Normal-Werte
Reticuloendothel	Reticulumzellen:			
	Makrophagen			—0,4
	plasmazelluläre	0,3		—1,0
	lymphoide			
	Endothelzellen:			
	Fettzellen:			
	Plasmazell. Mitosen		Besonderheiten:	
Erythropoëse	Proerythroblasten	9,0		—1
	Makroblasten	1,3		—1
	Normoblast basophil	54,3	103,3	—5 (10—20)
	polychrom	35,0		—15 (10—20)
	orthochrom	3,7		—5
	Erythrobl. Mitosen	3/310	Besonderheiten: Karyorrhexis	19/310
	Retikulocyten			
Leuko- und Lymphopoëse	Myeloblasten	0,3		—4
	unreife Myelocyten	6,0		-6
	halbreife Myelocyten	14,3 21,0		-12 (-25)
	reife Myelocyten	0,7		-12
	Metamyelocyten	7,7		-15
	Neutrophile stabk.	13,7 23,1		-40 (-60)
	segmentk.	1,7		-10
	Eosinophile I / III	3,0 / 2,0 5,0		—3 / —3 (—5)
	Basophile	–		—1
	Monocyten	8,0		—5
	Lymphoide Zellen	42,6		8—20
	(auf 100)			
	Mitosen –		Besonderheiten: Riesenneutrophile –	Toxisch: – –
	Unklare Zellen 88/610			
Thrombopoëse	Megakaryocyten (Zahl): vermindert / normal ++ / vermehrt –		unreif (+) / halbreif + / reif	Thrombocyten spärlich vorhanden / Riesenplättchen

Zellgehalt: Zellreiche Präp. mit sehr viel zerstörten Zellen

Beurteilung:

Erythroblasten sehr stark vermehrt, einige in Karyorrhexis

Reifere Neutro in mässiger Zahl

Monozyten vermehrt

Lymphoide Zellen vermehrt

Megakaryozyten z.T. stark segmentiert

Figure 5 Bone marrow examination of case 2.

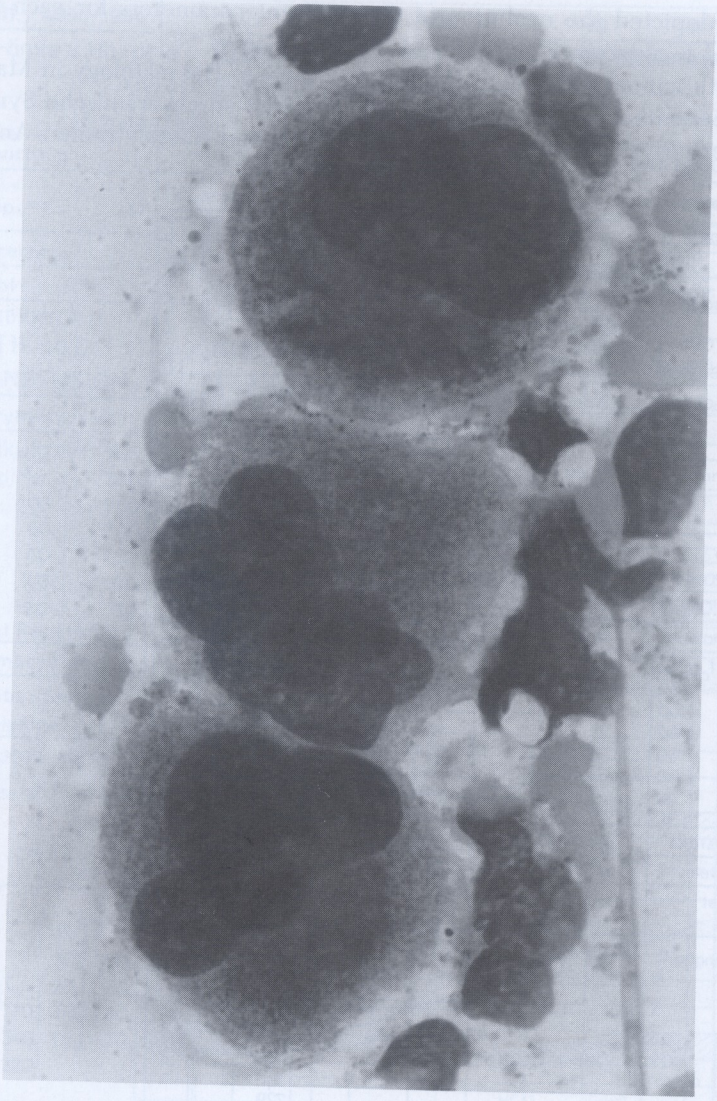


Figure 6 Three megacaryocytes in a bone marrow smear of case 1.

spital. These depicted the evolution of the different parameters for each patient. (Figures 7 and 8 concern patients 1 and 3.)

At the 10th annual meeting of the Swiss Society of Haematology in May 1955, Gasser and Siebenmann gave a paper entitled "Hämolytisch-urämische Syndrome, bilaterale Nierenrindennekrose bei akuten erworbenen hämolytischen Anämien."

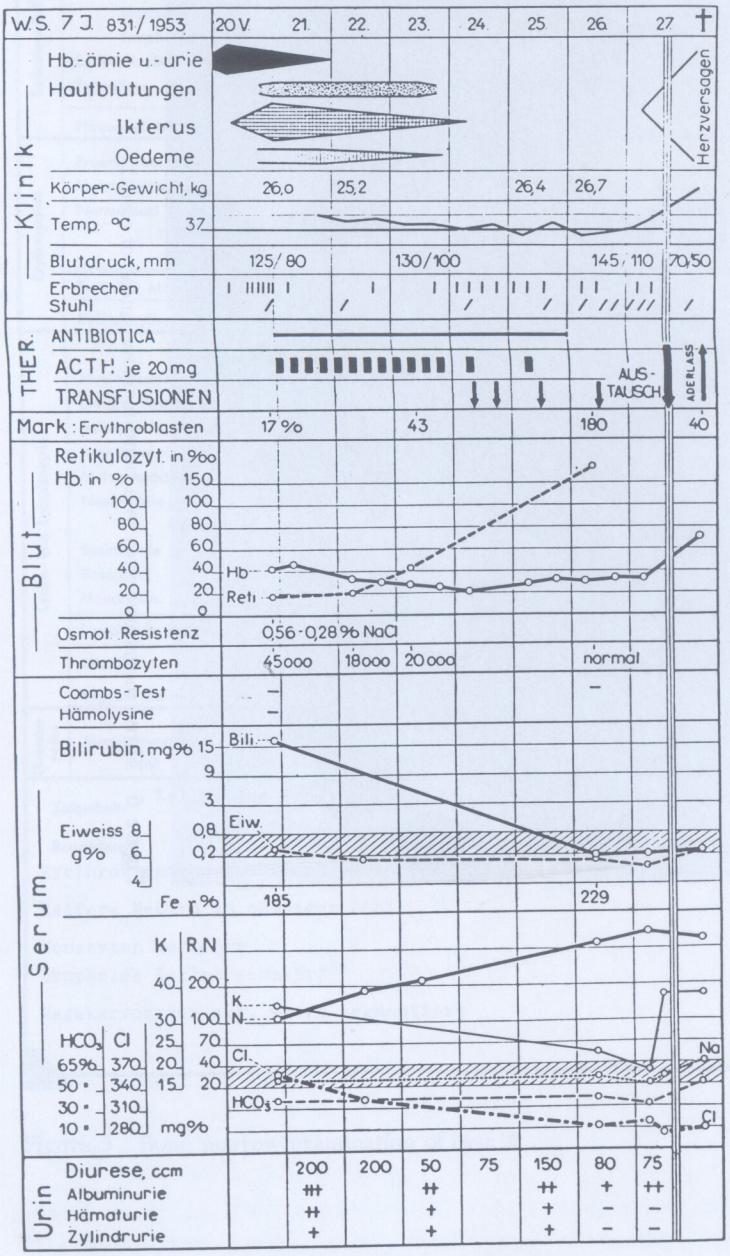


Abb. 1. Verlaufskurve zu Fall 1.

Figure 7 Graph of the evolution of case 1.

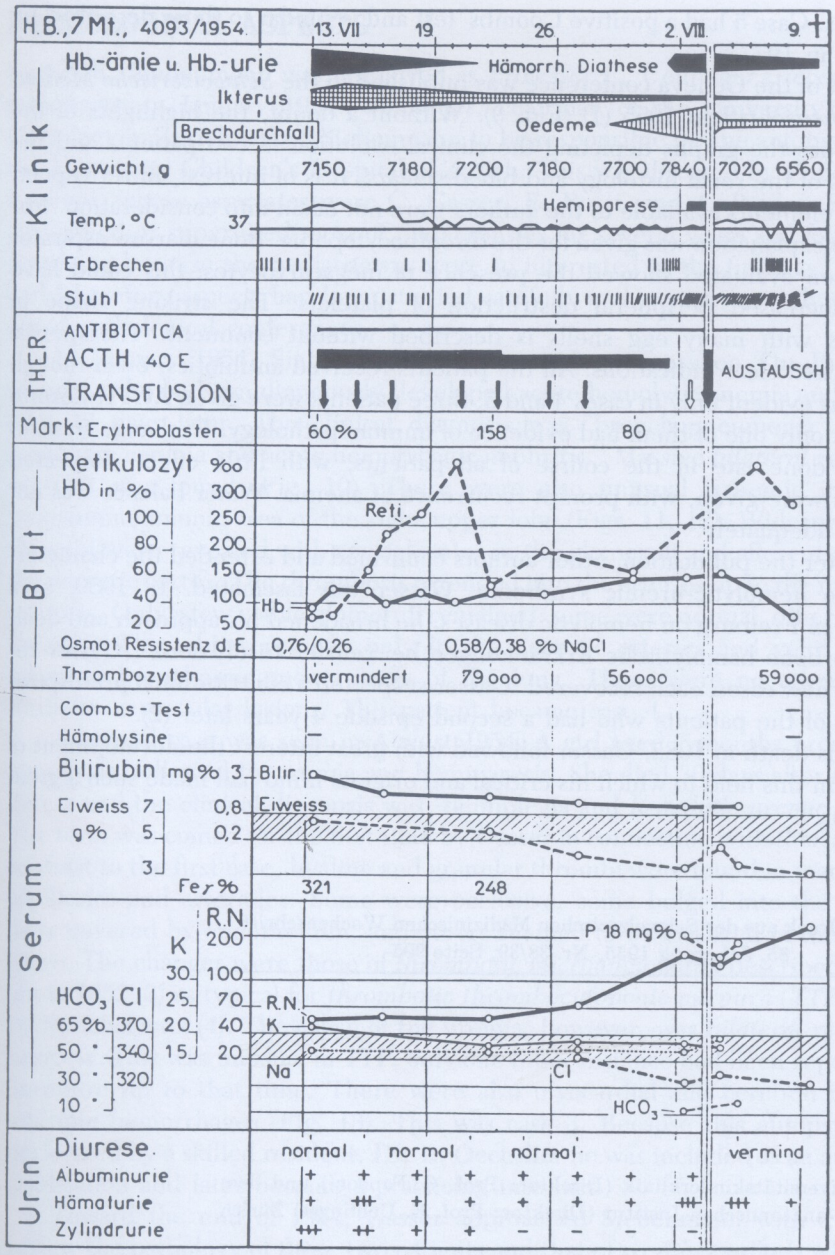


Abb. 4. Verlaufskurve zu Fall 3.

Figure 8 Graph of the evolution of case 3.

The striking appellation has become a classic. Gasser was extremely cautious. Not only did he use the term syndrome but applied the plural syndromes. Clearly certain characteristics were common to the five patients: the acquired hemolytic anemia, the renal failure (the cause of which was cortical necrosis), and the thrombocytopenia. On the other hand, the patients differed in age, course, involvement of other organs, and

pathogenesis. Case 5 had a positive Coombs' test and is similar to those described by Klein et al. in 1977.

The text of the Geneva conference was published in the *Schweizerische Medizinische Wochenschrift* in 1955 (1) (Fig. 9). Without a doubt, the highlights of the publication are the graphs depicting the clinical evolution in two patients and the photographs of the renal histology and blood smears. It is of interest, in retrospect, that certain elements available to the authors were not taken into consideration. For example, no explanation was given for the thrombocytopenia. Bone marrow aspirates that had been evaluated showed the presence of megacaryocytes; this could have suggested increased peripheral destruction of platelets. The striking shape of erythrocytes with many egg shells is described without comment. Therapeutic attempts lacked clear indications: All the patients received antibiotics, even though infection was evident only in cases 4 and 5; three patients were given ACTH despite the fact that only one of them had evidence of immunopathology. Exchange transfusions were done late in the course of all patients, with little effect. Repeated transfusions were given, with prompt recurrence of anemia. Water balance was not maintained adequately.

Soon after the publication, other authors confirmed and extended the characteristics of the hemolytic-uremic syndrome. Gasser was fascinated. In 1959, at a symposium in Freiburg on hemolytic diseases, he broadened his approach and dealt with "Erworbene hämolytische Erkrankungen bei renaler Insuffizienz". Gasser reported four new cases; each recovered. Gasser suspected a constitutional predisposition in one of the patients who had a second episode 4 years later (2).

Until his death in 1982, Gasser followed with great interest the development of knowledge in this field to which his critical and original mind had made such a great contribution.

Sonderabdruck aus der Schweizerischen Medizinischen Wochenschrift
85. Jahrgang 1955, Nr. 38/39, Seite 905

Aus der Universitätskinderklinik (Direktor: Prof. G. Fanconi) und dem pathologisch-anatomischen Institut (Direktor: Prof. E. Uehlinger) Zürich

Hämolytisch-urämische Syndrome: Bilaterale Nierenrindennekrosen bei akuten erworbenen hämolytischen Anämien*

Von C. Gasser, E. Gautier und Annemarie Steck (klinischer Teil) und R. E. Siebenmann und R. Oechslin (pathologisch-anatomischer Teil)

Figure 9 Title of the original paper on the hemolytic-uremic syndrome.

PATHOLOGICAL ASPECTS

Rudolf E. Siebenmann was employed as Professor E. Uehlinger's second associate pathologist in January 1954. Uehlinger, chairman of the University Institute of Pathology in Zurich, asked Siebenmann to be responsible for the autopsy service for the University Children's Hospital of Zurich. This was directed by Professor Guido Fanconi, whose associates were C. Gasser, E. Rossi, and A. Prader. Siebenmann performed or supervised most of the autopsies for several years and found the task gratifying because the pediatricians were so interested in the findings. The clinical and laboratory aspects had been studied carefully and were frequently discussed at clinicopathological conferences.

In January 1954, Siebenmann performed the autopsy on Th. Ruth, age 13 months, who had simultaneously developed acute hemolytic anemia and anuria and died 12 days later. The clinical diagnosis was "bronchopneumonia, acute toxic hemolytic anemia and acute hemorrhagic nephritis." Massive *bilateral renal cortical necrosis* was found (Fig. 10). There were also unusual ischemic infarcts in a bronchopneumonic area of the right upper lobe (Figs. 11, 12). Widespread hyaline thrombi were revealed with special stains in the glomeruli and afferent arterioles of the necrotic cortex. The thrombosis extended into the arteries up to the margin of the necrosis. Only a few viable glomeruli remained; some were normal, others had hyalin thrombi. Thrombi were seen only in the necrotic arteries and veins within the infarcted bronchopneumonic areas of the lung. There were no other extrarenal thrombi or vascular lesions. This patient became case 4.

A second case was seen in August 1954. A girl aged 7 months presented with hemolysis, followed by uremia and hemiparesis. She died 30 days after the onset of illness and the clinical diagnosis was "hemiplegia and *hemolytic uremic syndrome*." The term was coined for the first time by Gasser in connection with this fatal case. In contrast to the first case, hyaline and granular thrombi were found in many organs in capillaries and arterioles. Some were occlusive, some bulged into the lumen and were covered by endothelium, and others seemed to be localized in the subintimal space. The changes were those of *thrombotic microangiopathy* described by Symmers in 1952 (3) as typical for *thrombotic thrombocytopenic purpura (TTP)* described by Moschcowitz (4). The cause of the uremia, however, was *bilateral renal cortical necrosis*. This was unusual in TTP; only one other instance had been reported in the literature up to that time. There were also myocardial and cerebral infarcts and multiple hemorrhages (Fig. 13). This was case 3. Because this autopsy had been performed by a skilled resident, Dr. R. Oechslin, he was included as an author of the publication and later became a practicing internist.

Toward the end of 1954, Gasser approached Siebenmann with a request to review the pathology of these two patients and that of *six other infants* who had died with what he considered to be the same clinical entity of a "hemolytic uremic syndrome". In three of these six cases, the histopathological diagnosis had been "glomerular necrosis," "glomerular thrombosis with necrosis," and necrotizing acute glomerulonephritis." Glomerulonephritis was excluded in three cases because of bilateral cortical necrosis. The thrombosis of capillaries, arterioles, and some arteries was restricted to the kidneys. In one case, however, Siebenmann found the same peculiar anemic pulmonary infarcts in a preexisting bronchopneumonia as in the first case mentioned. These three patients had the full-blown clinical syndrome. In the

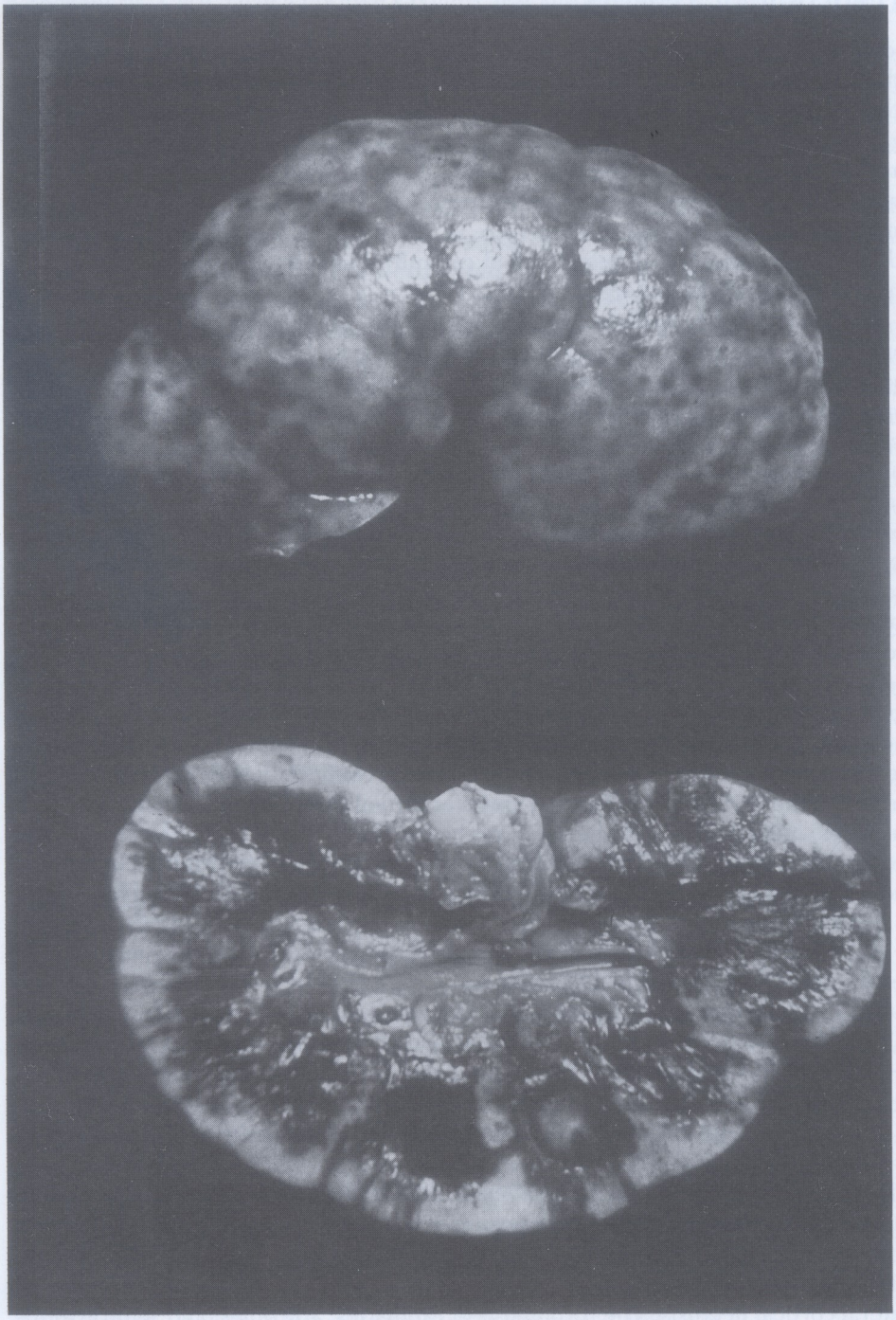


Figure 10 Massive bilateral cortical necrosis in case 4.

Figure 10 Massive bilateral cortical necrosis in case 4.

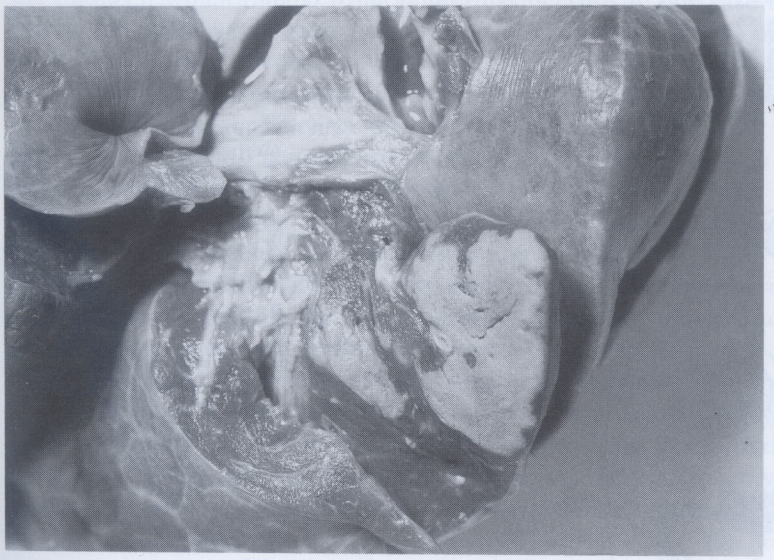


Figure 11 Ischemic infarcts in the lung of case 4.

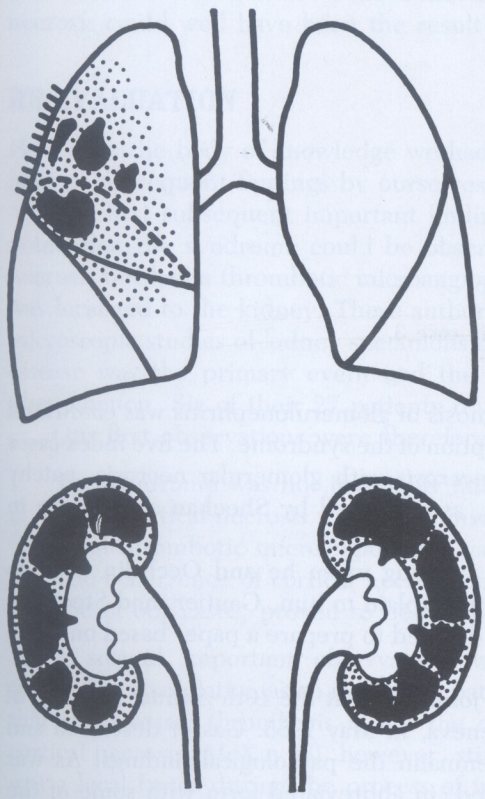


Figure 12 Drawing of the organs affected by infarcts in case 4.

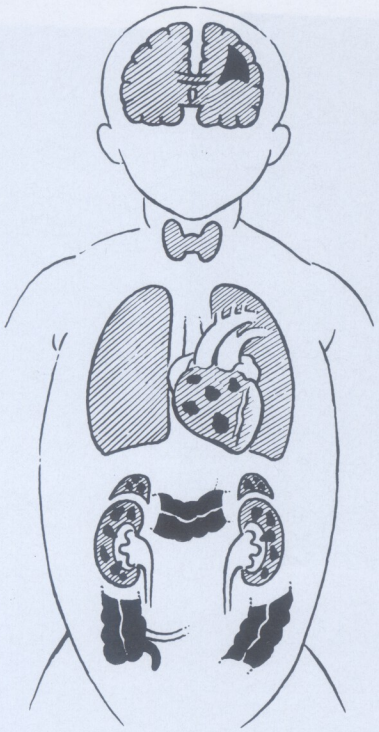


Figure 13 Drawing of the multiple lesions in case 3.

remaining three cases, however, the diagnosis of glomerulonephritis was confirmed and was not included in the original description of the syndrome. The five index cases all had variable *bilateral renal cortical necrosis* with glomerular necrosis, patchy necrosis, and massive confluent necrosis, as described by Sheehan and Moore in 1952 (5).

Siebenmann remembers one winter evening when he and Oechslin went to Gasser's office in the Children's Hospital to explain to him, Gautier, and Steck the pathology of renal cortical necrosis. They decided to prepare a paper based on these five selected cases.

Gasser and Siebenmann presented a joint paper at the 10th Annual Meeting of the Swiss Society of Haematology, in Geneva, in May 1955. Gasser described and discussed the clinical picture, and Siebenmann the pathological findings. As was traditional, the presentation was published, in abbreviated form with some of the illustrations, in the *Schweizerische Medizinische Wochenschrift* (1). They illustrated

the findings, which ranged from glomerular necrosis in one case to more extensive patchy necrosis in two cases and to massive confluent necrosis in two others. The thrombosis of capillary loops, of afferent arterioles, of radiate arteries in cases with more extensive necrosis, is always found in cortical necrosis and is an element of the diagnosis. This was not mentioned in the text of the publication but is illustrated in it, and Siebenmann still has the text of their Geneva paper in which he described the occurrence of thrombi with microscopic slides.

With the exception of the one patient (of Moschcowitz) who had TTP, no generalized intravascular thrombosis was found. Therefore, of the five patients with the hemolytic uremic syndrome, two only had renal cortical necrosis, two also had peculiar pulmonary infarcts in preexisting bronchopneumonia, and one had renal cortical necrosis and generalized thrombotic microangiopathy.

Although the cause of uremia was easily explained by the morphologic findings, Siebenmann was unable to determine a basis for the acute hemolysis. He could see only minor consequences of the hemolytic process with pigmented tubule casts and hemosiderosis in spleen and bone marrow. They excluded hemolysis-induced renal damage, as seen in the crush-kidney. Siebenmann accepted the views of Sheehan and Moore on the pathogenesis of the cortical necrosis; these authors considered spasm as the cause of the thrombi in the small vessels. He had no explanation for the pulmonary infarcts except for an arteritis occurring in association with bronchopneumonia. He excluded an embolic process. The question of shock induced by hemolysis was raised at the Geneva meeting, and they agreed that the renal cortical necrosis could well have been the result of severe shock.

RE-EVALUATION

How does the body of knowledge we had assembled in 1955 look in retrospect, in light of subsequent findings by ourselves and others?

The first subsequent important finding was by Habib et al. in 1958 (6). They noted that the syndrome could be observed in infants who did not have cortical necrosis but had a thrombotic microangiopathy or arteriolocapillary thrombosis that was localized to the kidney. These authors later suggested, on the basis of electron microscopic studies of kidney specimens obtained by renal biopsy, that the vascular disease was the primary event and the thrombosis was a subsequent secondary phenomenon. Six of their 27 patients reviewed in 1967 survived (7).

Our first observations were therefore expanded and corrected:

1. The syndrome was not invariably fatal.
2. Renal cortical necrosis was not an invariable finding. On the contrary, localized renal thrombotic microangiopathy was more frequent, even in fatal cases.
3. The occurrence of cortical necrosis in the context of TTP (Moschcowitz), as in one of our cases, proved to be unusual.

A second important observation was the recognition of disseminated intravascular coagulation as an important pathogenetic mechanism (8, 9). It now seems that small-vessel thrombosis is not the consequence, but the cause of the renal cortical necrosis. McKay (8), however, still thought that spasm of the renal arteries was a local factor during the process of intravascular coagulation.

It was also claimed that the thrombotic microangiopathy might be the manifesta-

tion of a primary coagulation process with secondary changes in vessel walls. This theory is supported by the observation that paraneoplastic microthrombosis, which is not a primary vascular disease, leads to the same pathologic changes in vessels as idiopathic thrombotic microangiopathy (10). We still think that the concept that the deciding event is a primary intravascular coagulation has not been excluded (9). Fibrinolysis, which occurs very quickly in vessels and tissues, even postmortem, may lyse many thrombi and thereby render their detection impossible.

A third important finding was that acute hemolysis was the result of mechanical fragmentation of the erythrocytes (11). These workers showed that the typical changes of red blood cells observed by Gasser could be produced by fibrin strands or endothelial lesions. The erythrocyte fragmentation has been observed in other instances of renal cortical necrosis and shock and other causes of intravascular coagulation. Confirmation of this pathogenetic mechanism was not possible in our histological studies and has never been observed in tissue sections from cases of HUS. Interestingly, the fragmentation of erythrocytes was described by Rindfleisch, a professor of pathology in Zurich, in 1891. He thought it was due to mechanical impacts. Ehrlich (12), who mentions this in 1891, considered that it was caused by a chemical process.

CONCLUSION

In conclusion, it is not unusual that the detection and first description of a new syndrome is based on the observation of the most severe form of the disease, so that the less severe nonfatal forms, which fortunately occur more frequently, are noted only later. The observation of this unique clinical syndrome by Gasser triggered many important clinical, pathological, and experimental studies which were of a great importance in general pathology. Siebenmann is pleased that a pathologist contributed to the characterization and delimitation of the syndrome and has always thought that this work was a good example of fruitful clinicopathological cooperation.

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