February 13, 1964

THE PORPHYRIAS - RECENT ADVANCES

Case presentation: [redacted] [redacted]

This 32-year old woman was apparently in good health until [redacted] 1963 when she began to have abdominal pain of a generalized nature associated with vomiting, dizziness, and muscle aches. On [redacted] she was hospitalized at another institution where physical examination was said to be normal except for tanning of the skin and hypoactive tendon reflexes. Over a four-day period colicky pain continued with occasional episodes of disorientation and vomiting. On [redacted] following completion of an upper GI series, she had a grand mal seizure. She was given Dilantin and pentobarbital. Lumbar puncture showed an opening pressure of 23 cm of HOH. Two lymphocytes were seen and total protein was reported as 10.2 mg%. The following day the urine was tested for porphobilinogen with negative results. Forty-eight hours after th convulsion a repeat test was said to be strongly positive for porphobilinogen. Barbiturates were discontinued and chlorpromazine therapy was started with some subjective improvement in pain noted. Despite this therapy the patient developed progressive weakness of the legs, abdomen, and arms and subsequently had difficulty in swallowing. On [redacted] her blood pressure decreased to 80/50 and respirations became labored. At this point 100 mg of hydrocortisone was administered and the patient was transferred to Parkland Memorial Hospital. Accompanying laboratory data indicated that the patient had a hemoglobin of 12.0 Gms%. Two white blood cell counts had been obtained of 6,500 and 12,300, both with normal differentials. Of particular interest were the serum electrolyte values recorded below:

	[redacted]	[redacted]	[redacted]
BUN	34	37	-
Na	100	128	138
K	3.0	4.1	6.5
Cl	94	81	94
CO_2	-	32	-
Ca	5.3	-	-

Urine specific gravity on [redacted] was 1.020. The nature of fluid therapy in the interval prior to transfer is not known.

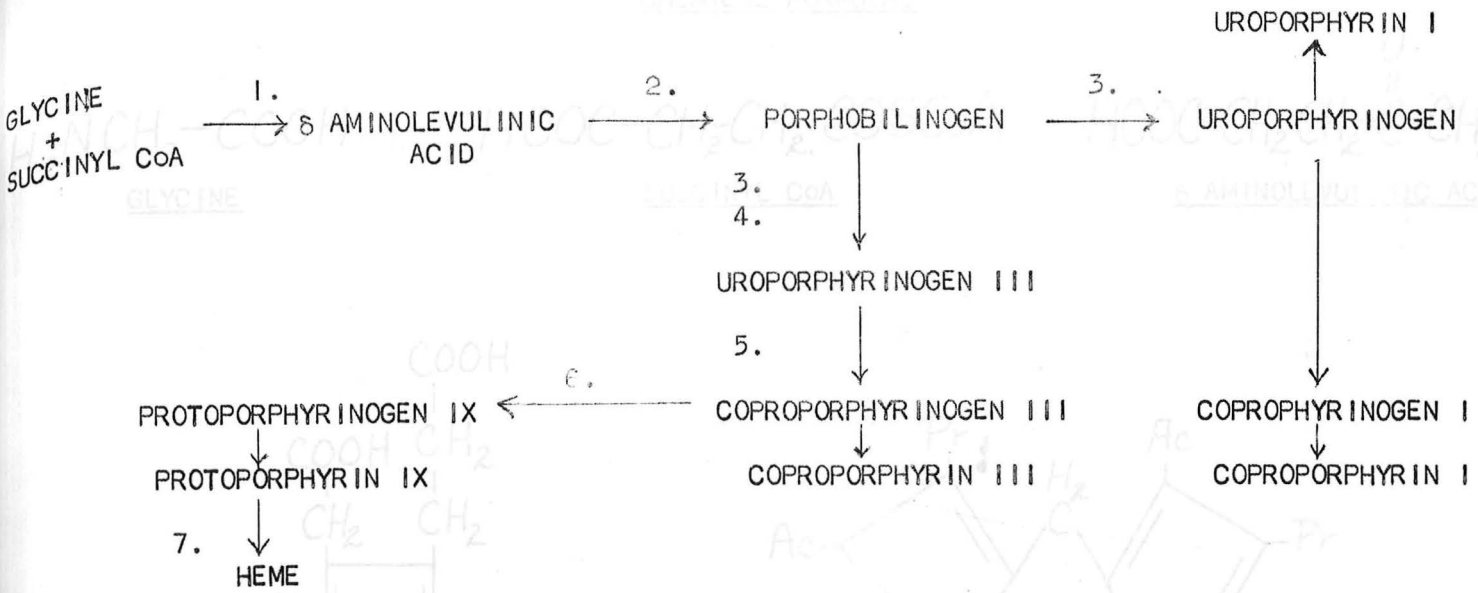
On arrival at [redacted] the patient was noted to be almost completely flaccid from the upper chest down. She was tachypneic and showed decreased skin turgor. While conscious she was described as communicating poorly. Pulse was 134, respirations were 36 and shallow and blood pressure was 114/70. The skin was noted to be tanned. Only the upper chest expanded with respiration and breath sounds were not heard over the lower half of the lung fields. No dullness or rales were noted. The heart was normal except for the tachycardia. The abdomen was soft and flaccid with decreased bowel sounds. The liver and spleen were not felt. Complete flaccid paralysis of both legs was noted with absent stretch reflexes. Pain and touch sensations were absent. Cranial nerves V, VII, IX, X, XI, and XII were involved bilaterally.

Additional history was obtained that the patient had had periodic vesicular eruptions of the hands for a number of years. A sister with similar skin manifestations had been hospitalized on at least one occasion with cramping abdominal pain "due to nerves". The mother had a history of grand mal seizures associated with "orange urine".

Shortly after admission a tracheostomy was performed and respiration supported with an intermittent positive pressure respirator. The extracellular fluid volume deficit was replenished with isotonic saline. On the second hospital day the systolic blood pressure decreased to 80 and hydrocortisone therapy was started with apparent pressor response. Despite a slight initial improvement the patient developed a fever of 103° and showed periodic Cheyne-Stokes respiration. Tachycardia of 120 to 150 beats per minute was constant. Blood, sputum, and urine cultures were obtained and chloramphenicol and Kanamycin therapy was started. On the fourth hospital day chest x-ray showed patchy infiltrates throughout both lung fields. A technical failure in supported respiration occurred on the same day with a brief cardiac arrest which responded to closed chest massage and IV adrenalin. Azotemia was progressive despite urine outputs recorded between 1000 and 2000 cc per 24 hours. On the sixth hospital day one of three blood cultures was positive for a gram negative rod sensitive to Colistin. The latter drug and Staphcillin were started. Despite all measures the patient became progressively worse, developed profound shock unresponsive to vasopressor agents and died on [redacted] 1963. A summary of the laboratory data follows:

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb	13.1	12.4	12.5			11.8	10.2	10.0	12.0
Hct		35		35	34			29	
WBC	8,450	10,000	9,800			18,200	20,700	17,100	18,500
BUN	42	50	74	90	98	105	110	110	95
CO_2	28	25	28	23	23	18	20	17	17
Cl	98	100	105	100	106	111	109	119	113
Na	133	136	143	137	139	141	140	146	145
K	5.3	4.2	3.8	4.4	5.1	4.3	5.0	5.5	5.4
Blood pH	7.40				7.44		7.40		
Oxygen sat.	98%								
CO_2 tension	46				29		29		
Albumin		3.4							
Globulin		2.4							
Bilirubin		0.6							
Prothrombin		90%							
Ceph. floc.		3+							
Porphobilinogen	Positive								

PORPHYRIN BIOSYNTHESIS

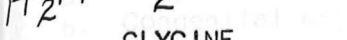


1. δ Aminolevulinic acid synthetase
2. δ Aminolevulinic acid dehydrase
3. Uroporphyrinogen I synthetase (Uro I deaminase)
4. Uroporphyrinogen III cosynthetase (Uro I isomerase)
5. Uroporphyrinogen decarboxylase
6. Coproporphyrinogen decarboxylase (oxidase)
7. Protoporphyrin ferrochelatase

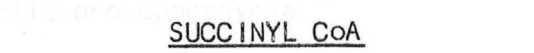
NORMAL EXCRETORY VALUES (maximum)

	Urine	Feces
Uroporphyrin	30 μG/liter	2 μG/g dry weight
Coproporphyrin	211 μG/liter	20 μG/g dry weight
Protoporphyrin	-	40 μG/g dry weight
Porphobilinogen	2 mg/liter	-
δ Aminolevulinic acid	6 mg/liter	-

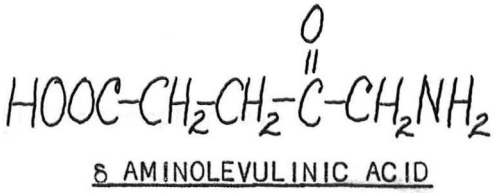
CHEMICAL FORMULAS



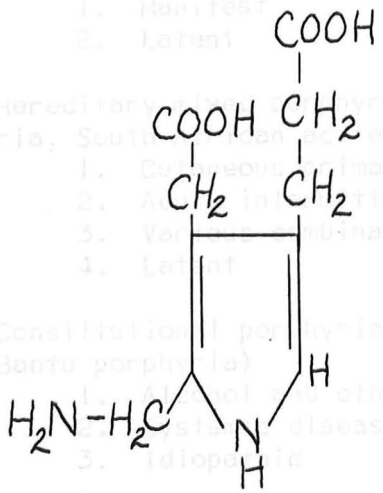
GLYCINE



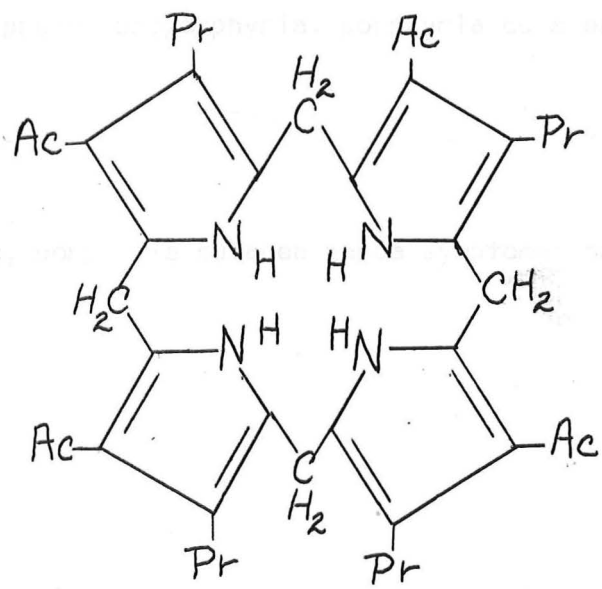
SUCCINYL CoA



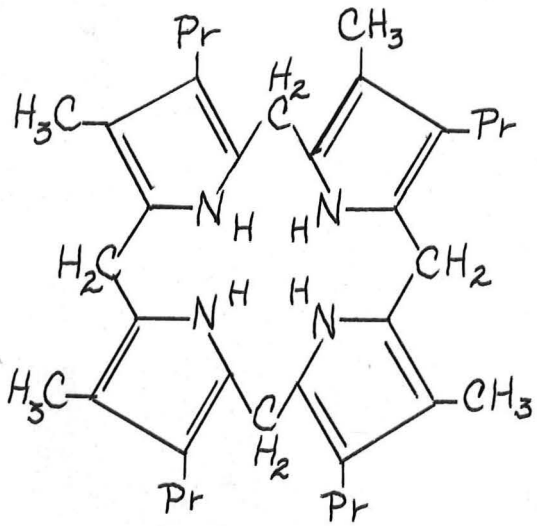
δ AMINOLEVULINIC ACID



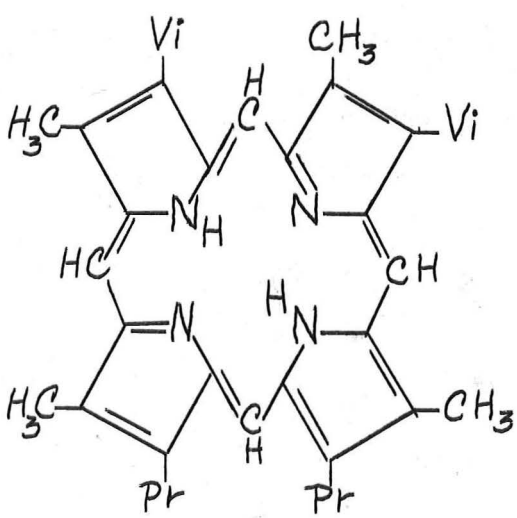
PORPHOBILINOGEN



UROPORPHYRINOGEN III



COPROPORPHYRINOGEN III



PROTOPORPHYRIN-9

CLASSIFICATION OF THE PORPHYRIAS

I. Erythropoietic Porphyria

a. Congenital erythropoietic porphyria (Congenital erythropoietic uroporphyria)
b. Congenital erythropoietic protoporphyria

II. Hepatic Porphyria

a. Hereditary acute intermittent porphyria (Swedish acute intermittent)
    1. Manifest
    2. Latent

b. Hereditary mixed porphyria (Variegate, protocoproporphyria, porphyria cutanea tarda hereditaria, South African acute intermittent)
    1. Cutaneous primarily
    2. Acute intermittent primarily
    3. Various combinations
    4. Latent

c. Constitutional porphyria (Idiosyncratic, porphyria cutanea tarda symptomatica, South African Bantu porphyria)
    1. Alcohol and other chemicals
    2. Systemic diseases
    3. Idiopathic

d. Acquired porphyria
    1. Hepatoma
    2. Hexachlorobenzene

CHARACTERISTICS OF THE PORPHYRIAS

Type	Inheritance	Anemia	Cutaneous	Neurological	Urine	Feces
Congenital Erythropoietic	Recessive	+	+	-	↑Uro I ↑Copro I	Normal to slight ↑ Uro I Copro I
Congenital Protoporphyria	?	+ -	+	-	↑Copro	↑Proto ↑Copro
Hereditary Intermittent	Dominant	-	-	+	↑PBG ↑ALA (constant)	Slight↑Copro ↑Proto (acute) Normal (remission)
Hereditary Mixed	Dominant	-	rare ♀ common ♂	common ♀ rare ♂	↑PBG ↑ALA (acute episode only)	↑Copro ↑Proto ↑Uro (constant, less during acute episode)
Constitutional	Non-Hereditary	-	+	+ -	↑Uro	Normal to Slight ↑ Uro and Copro
Acquired	Non-hereditary	-	+	-	↑PBG ↑ALA ↑Uro ↑Copro	Slight to moderate ↑ Uro and Copro

PBG=porphobilinogen ALA=δ aminolevulinic acid COPRO=coproporphyrin *URO=uroporphyrin*
PROTO=protoporphyrin

SIGNS AND SYMPTOMS - THE ACUTE ATTACK

	Waldenstrom (233 cases)[50]	Goldberg (50 cases)[49]	Markovitz (69 cases)[51]	Eales (80 cases)[48]
	percent	percent	percent	percent
Males	40	38	39	30
Females	60	62	61	70
Abdominal pain	85	94	95	90
Vomiting	59	78	52	80
Mental changes	55	56	80	55
Constipation	48	74	46	80
Paralysis	42	68	72	53
Hypertension	40	56	49	55
Pyrexia	37	14	36	38
Tachycardia	28	64	51	83
Seizures	10	18	-	12
Sensory loss	9	38	24	15
Diarrhea	9	12	11	8
Azotemia	9	-	67	69
Proteinuria	9	14	-	8
Leukocytosis	7	24	48	20
Blindness	4	3	-	3
Cranial nerves	-	29	51	9
ECG abnormalities	-	44	47	23

REFERENCES

* Articles of particular interest

REVIEWS

* 1. Schmid, R., "Diseases of Porphyrin Metabolism" in The Metabolic Basis of Inherited Disease, J. B. Stanbury, J. B. Wyngaarden, and D. S. Frederickson, Eds. McGraw-Hill 1960, p. 939.
2. Saint, E. G., "The Porphyrinopathies". Med. J. Austr. 1:101, 1963.
3. Margoliash, E., "Porphyrins and Hemoproteins". Ann. Rev. Biochem. 30:549, 1961.
4. Eales, L., "The Porphyrins and the Porphyrias". Ann. Rev. Int. Med. 12:251, 1961.

BIOCHEMISTRY and REGULATION

5. Neuberger, A., Muir, H. M. and Gray, C. H., "Biosynthesis of Porphyrins and Congenital Porphyria". Nature 165:948, 1950.
6. Cookson, G. H. and Rimington, C., "Porphobilinogen". Biochem. J. 57:476, 1954.
7. Shemin, D., "The Succinate-Glycine Cycle; The Role of δ-Aminolevulinic Acid in Porphyrin Synthesis", in Porphyrin Biosynthesis and Metabolism, p. 4, Ciba Foundation, London, 1955.
* 8. Granick, S., "Porphyrin Biosynthesis, Porphyria Diseases, and Induced Enzyme Synthesis in Chemical Porphyria". Tr. N. Y. Acad. Sci. 25:53, 1962.
9. Schwartz, H. C., Goudsmit, R., Hill, R. L., Cartwright, G. E. and Wintrobe, M. M., "The Biosynthesis of Hemoglobin from Iron, Protoporphyrin, and Globin". J. Clin. Invest. 40:188, 1961.
10. Mauzerall, D. and Granick, S., "The Occurrence and Determination of δ-Aminolevulinic Acid and Porphobilinogen in Urine". J. Biol. Chem. 219:435, 1956.
11. Gibson, K. D., Matthew, M., Neuberger, A. and Tait, G. H., "Biosynthesis of Porphyrins and Chlorophyll". Nature 192:204, 1961.
12. Porra, R. J. and Jones, O. T. G., "Studies on Ferrochelatase". Biochem. J. 87:181, 1963.
13. Gibson, K. D., Neuberger, A. and Tait, G. H., "Studies on the Biosynthesis of Porphyrin and Bacteriochlorophyll by Rhodopseudomonas Spheroides". Biochem. J. 83:539, 1962.
* 14. Burnham, B. F. and Lascelles, J., "Control of Porphyrin Biosynthesis Through a Negative-Feedback Mechanism". Biochem. J. 87:462, 1963.
* 15. Granick, S., "Induction of the Synthesis of δ-Aminolevulinic Acid Synthetase in Liver Parenchymal Cells in Culture by Chemicals That Induce Acute Porphyria". J. Biol. Chem. 238:PC 2247, 1963.
16. Onisawa, J. and Labbe, R. F., "δ-Aminolevulinate Dehydratase Activity in Liver and Its Relation to Substrate Concentration". Biochim. Biophys. Acta 56:618, 1962.
17. Sano, S. and Granick, S., "Mitochondrial Coproporphyrinogen Oxidase and Protoporphyrin Formation". J. Biol. Chem. 236:1173, 1961.

PHYSIOLOGY and PHARMACOLOGY

* 18. Sano, S. and Rimington, C., "Excretion of Various Porphyrins and Their Corresponding Porphyrinogens by Rabbits After Intravenous Injection". Biochem. J. 86:203, 1963.
19. Richards, F. F. and Scott, J. J., "Glycine Metabolism in Acute Porphyria". Clin. Sci. 20:387, 1961.
20. Olsson, R. A., and Ticktin, H. E., "Zinc Metabolism in Acute Intermittent Porphyria". J. Lab. Clin. Med. 60:48, 1962.

21. Berlin, N. I., Neuberger, A., and Scott, J. J., "The Metabolism of δ-Aminolevulinic Acid". Biochem. J. 64:80, 1956.
* 22. Goldberg, A., Paton, W. D. M., and Thompson, J. W., "Pharmacology of the Porphyrins and Porphobilinogen". Brit. J. Pharmac. 9:91, 1954.

EXPERIMENTAL PORPHYRIA

23. Haeger-Aronsen, B., "Porphyria Induced in the Rat by Diethyl-1,4-dihydro-2,4,6-trimethyl-pyridine-3,5-dicarboxylate". Acta Pharmacol. et Toxicol. 18:165, 1961.
24. Dowdle, E. B. and Eales, L., "The Metabolism of Glycine in Experimental Porphyria". S. Afr. J. Lab. Clin. Med. 9:5, 1963.
25. Lottsfeldt, F. I., Labbe, R. F., and Aldrich, R. A., "Effect of Inosine on Heme Synthesis in Experimental Porphyria". J.A.M.A. 178:160, 1961.
26. Talman, E. L., Labbe, R. F., Aldrich, R. A., and Sears, D., "Porphyrin Metabolism V. The Metabolism of Purines in Experimental Porphyria". Biochim. Biophys. Acta 80:446, 1957.
27. Rose, J. A., Hellman, E. S., and Tschudy, D. P., "Effect of Diet on Induction of Experimental Porphyria". Metabolism 10:541, 1961.
28. Tschudy, D. P., Rose, J. A., Hellman, E. S., Collins, A. and Rechcigl, M. Jr., "Biochemical Studies of Experimental Porphyria". Metabolism 11:1287, 1962.
29. DeMatteis, F., Slater, T. F., and Wang, D. Y., "Liver Nucleotides in Experimental Hepatic Porphyria". Biochim. Biophys. Acta 68:100, 1963.
30. Ockner, R. K. and Schmid, R., "Acquired Porphyria in Man and Rat Due to Hexachlorobenzene Intoxication". Nature 189:499, 1961.
31. DeMatteis, F., and Prior, B. E., "Experimental Hepatic Porphyria Caused by Feeding 3,5-Diethoxycarbamyl-1,4-dihydro-2,4,6-trimethylpyridine". Biochem. J. 83:1, 1962.
32. Labbe, R. F., Hanowa, Y. and Lottsfeldt, F. I., "Heme and Fatty Acid Biosynthesis in Experimental Porphyria". Arch. Biochem. Biophys. 92:373, 1961.
33. DeMatteis, F. and Rimington, C., "Disturbances of Porphyrin Metabolism Caused by Griseofulvin in Mice". Brit. J. Derm. 75:91, 1963.

CLASSIFICATIONS

34. Editorial, "Porphyria", Lancet 1:926, 1961.
35. Scolari, E. G., "Porphyria Congenita and Porphyria Cutanea Tarda". Panminerva Med. 4:323, 1962.
* 36. Watson, C. J., "The Problem of Porphyria - Some Facts and Questions". N. Eng. J. Med. 263:1205, 1960.
* 37. Dean, G. and Barnes, H. D., "Porphyria in Sweden and South Africa". S. Afr. Med. J. 33:246, 1959.
* 38. Schmid, R., Schwartz, S., and Watson, C. J., "Porphyrin Content of Bone Marrow and Liver in the Various Forms of Porphyria". Arch. Int. Med. 93:167, 1954.

HYPOTHESES AS TO DEFECTS

39. Rimington, C., "Types of Porphyria: Some Thoughts About Biochemical Mechanisms Involved". Ann. N. Y. Acad. Sci. 104:666, 1963.
40. Bogorad, L., "Enzymatic Mechanisms in Porphyrin Synthesis: Possible Enzymatic Blocks in Porphyria". Ann. N. Y. Acad. Sci. 104:676, 1963.
41. DeMatteis, F., and Rimington, C., "An Hypothesis Concerning the Biochemical Disturbance in Acute Intermittent and Experimental Porphyria". Lancet 1:1332, 1962.

CLINICAL

1. Erythropoietic Porphyria

42. Schmid, R., Schwartz, S., and Sundberg, R. D., "Erythropoietic (Congenital) Porphyria: A Rare Abnormality of the Normoblasts". Blood 10:416, 1955.

43. Larizza, P., "The Problem of Erythropoietic Porphyria in the Light of the Latest Advances in Biochemistry and Morphology". Panminerva Med. 4:315, 1962.
44. Magnos, I. A., Jarrett, A., Prankerd, T. A. J., and Rimington, C., "Erythropoietic Protoporphyria. A New Porphyria Syndrome with Solar Urticaria Due to Protoporphyrinaemia". Lancet 2:448, 1961.
45. Porter, F. S., and Lowe, B. A., "Congenital Erythropoietic Protoporphyria". Blood 22:521, 1963.
46. Berke, M., and Redeker, A. G., "Erythropoietic Protoporphyria with Eczema Solare: Report of 3 Cases". Arch. Derm. 87:507, 1963.

II. Hepatic Porphyria

48. Eales, L., and Linder, G. C., "Porphyria - The Acute Attack". S. Afr. Med. J. 36:284, 1962.
49. Goldberg. A., "Acute Intermittent Porphyria". Quart. J. Med. 28:183, 1959.
50. Waldenstrom, J., "The Porphyrias as Inborn Errors of Metabolism". Amer. J. Med. 22:758, 1957.
51. Markovitz, M., "Acute Intermittent Porphyria: A Report of Five Cases and a Review of the Literature". Ann. Int. Med. 41:1170, 1954.
52. Ludwig, G. D., and Goldberg, M., "Hyponatremia in Acute Intermittent Porphyria Probably Resulting From Inappropriate Secretion of Antidiuretic Hormone". Ann. N. Y. Acad. Sci. 104:710, 1963.
53. Hellman, E. S., Tschudy, D. P., and Bartter, F. C., "Abnormal Electrolyte and Water Metabolism in Acute Intermittent Porphyria". Amer. J. Med. 34:734, 1962.
54. Waldenstrom, J., and Haeger, B., "The Liver and Cutanea Tarda". Ann. Int. Med. 53:286, 1960.
55. Richards, F. F., and Brinton, D., "Peripheral Neuropathy and the Diagnosis of Acute Porphyria". Brain 85:657, 1962.
56. Ludwig, G. D., and Epstein, I. S., "A Genetic Study of Two Families Having the Acute Intermittent Type of Porphyria". Ann. Int. Med. 55:81, 1961.
57. Watson, C. J., and Cardinal, R., "Acute Intermittent Porphyria". J.A.M.A. 175:135, 1961.
58. Burnett, J. W., and Pathak, M. A., "Pathogenesis of Cutaneous Sensitivity in Porphyria". N. Eng. J. Med. 268:1203, 1963.
59. Bell, W. G. M., and Warnock, C. G., "Sunlight and the Skin". Lancet 1:774, 1963.
60. Editorial, "Griseofulvin and Porphyrin Metabolism". Lancet 1:870, 1963.
61. Cain, C., and Nigogosyan, G., "Acquired Toxic Porphyria Cutanea Tarda". J.A.M.A. 183: 90, 1963.
62. Sweeney, G. D., Levey, M., Dowdle, E. B., and Eales, L., "The Effects of Chloroquine on Patients with Symptomatic Porphyria". S. Afr. Med. J. 36:312, 1962.
63. Barnes, H. D., "Acquired Porphyria in White Patients". S. Afr. Med. J. 37:412, 1963.
64. Denny-Brown, D., and Sciarra, D., "Changes in the Nervous System in Acute Porphyria". Brain 68:1, 1945.
65. Ten Eyck, F. W., Martin, W. J., and Kernoban, J. W., "Acute Porphyria: Necropsy Studies in Nine Cases". Proc. Staff Meet. Mayo Clinic 36:1, 1961.
66. Lamont, N. M., Hatborn, M., and Joubert, S. M., "Porphyria in the African". Quart. J. Med. 30:373, 1961.
67. Dean, G., and Barnes, H. D., "The Inheritance of Porphyria". Brit. Med. J. 32:89, 1955.
68. Tio (Tiong Hoo), Leijuse, B., Jarrett, A., and Rimington, C., "Acquired Porphyria from a Liver Tumor". Clin. Sci. 16:517, 1957.

LABORATORY FINDINGS

69. Eales, L., and Saunders, S. J., "The Diagnostic Importance of Faecal Porphyrins in the Differentiation of the Porphyrias. I. Values in Normal Subjects and in Patients with Non-Porphyria Diseases". S. Afr. J. Lab. Clin. Med. 8:127, 1962.
70. Goodman, R. S., and Lyon, L. J., "Screening Tests for Urinary Uroporphyrin". J.A.M.A. 182:1087, 1962.
71. Ackner, B., Cooper, J. E., Gray, C. H., Kelly, M., and Nicholson, D. C., "Excretion of Porphobilinogen and δ-Aminolevulinic Acid in Acute Porphyria". Lancet 1:1256, 1961.
72. Eales, L., Dowdle, E. P., Saunders, S. J., and Sweeney, G. D., "The Excretion of δ-Aminolevulinic Acid and Porphobilinogen in the Acute Attack of Protocoproporphyria". S. Afr. Med. J. 37:100, 1963.
73. Falk, J. E., "Chromatography of Porphyrins and Metalloporphyrins". J. Chromat. 5:277, 1961.
74. Granick, S., and Vanden Schrreck, H. G., "Porphobilinogen and δ-Aminolevulinic Acid in Acute Porphyria". Proc. Soc. Exper. Biol. Med. 88:270, 1955.
75. Barnes, H. D., "The Excretion of Porphyrins and Porphyrin Precursors by Bantu Cases of Porphyria". S. Afr. Med. J. 33:274, 1959.
76. Haeger, B., "Urinary δ-Aminolevulinic Acid and Porphobilinogen in Different Types of Porphyria". Lancet 2:606, 1958.
77. Haeger-Aronsen, B., "Fecal Porphyrins in Porphyria Acuta, Porphyria Cutanea Tarda, and Intoxicato plumbi". Scand. J. Clin. Lab. Invest. 14:397, 1962.

TREATMENT

78. Kiger, R. G , "Observations in the Symptomatic Treatment of Porphyria with Valemate Bromide". South Med. J. 55:154, 1962.
79. Gajdos, A., and Gajdos-Torok, M., "The Therapeutic Effect of Adenosine-5-Monophosphoric Acid in Porphyria". Lancet 2:175, 1961.
80. Gajdos, A., "Clinical and Experimental Trial of Adenosine-5-Monophosphoric Acid in Porphyria". Panminerva Med. 4:332, 1962.
81. Berg, M., "Acute Porphyria". Arch. Int. Med. 76:335, 1945.
82. "Medical Grand Rounds at the Massachusetts General Hospital", Amer. Pract. Dig. Treat. 11:883, 1960.
83. Janoff, L. A., Poutas, J. J., and Young, D., "Acute Intermittent Porphyria". Arch. Int. Med. 91:389, 1952.
84. Gillespy, R. O., and Smith, S. G., "Porphyria Treated with Neostigmine". Lancet 1:908,
85. Melby, J. C., Street, J. P., and Watson, C. J., "Chlorpromazine in the Treatment of Porphyria". J.A.M.A. 162:174, 1956.
86. Broomfield, B., "Acute Intermittent Porphyria Treated With Chlorpromazine". Proc. Roy. Soc. Med. 55:799, 1962.
87. Peters, H. A., "Trace Metals, Chelating Agents, and the Porphyrias". Fed. Proceed. 20: 232, 1961 (part 2).