COPROPORPHYRIA*

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At the International Conference on the Porphyrias held in Cape Town in September 1963, agreement on the classification of the porphyrias was reached. However, this classification did not include coproporphyria.[1] The porphyrias were classified at the conference as follows:

The Hepatic Porphyrias

1. *Acute intermittent porphyrias* (pyrrolo-porphyria or Swedish genetic porphyria). This is the non-sex-linked Mendelian-dominant porphyria which has been so well described by Waldenström in Sweden.[2] In acute intermittent porphyria, acute attacks may be precipitated by certain drugs, particularly barbiturates and sulphonamides, but cutaneous lesions do not occur. It may be recognized by the presence of porphobilinogen in the urine, as indicated by the Watson-Schwartz test, even during the quiescent phase in adults.[3] There is usually little or no increase in faecal porphyrin.

2. *Porphyria variegata* (protoporphyria or South African genetic porphyria). This is the non-sex-linked Mendelian-dominant porphyria that is very common among the White population of Southern Africa; it also occurs in Europe and North America. In this type both acute attacks and cutaneous lesions may occur. The Watson-Schwartz test is generally positive only during an acute attack, but there is usually a great increase in porphyrin in the stool. The stool porphyrin consists of protoporphyrin and coproporphyrin, which are usually at the same general level.[4]

3. *The purely cutaneous porphyrias.* These include, in the first place, the possibly genetically predisposed type but not obviously inherited (porphyria cutanea tarda, symptomatic porphyria). It is usually associated with the abuse of alcohol and it is very common among the non-White population in South Africa.[5]

The undoubtedly acquired types, e.g. hexachlorobenzine-induced porphyria (Turkish toxic porphyria in children) form the second group.[6]

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There is not yet agreement whether an inherited, purely cutaneous, hepatic porphyria exists other than porphyria variegata. In these purely cutaneous porphyrias the urine is dark in colour and contains a great excess of porphyrin but there is little or no increase in porphobilinogen or in the faecal porphyrin.

Erythropoietic Porphyrias

1. *Congenital erythropoietic porphyria.* It causes cutaneous symptoms, anaemia and splenomegaly in infancy.[7]

2. *Erythropoietic protoporphyria.* It causes an urticaria-like rash.[8]

At the Cape Town conference there was disagreement as to whether or not a hereditary coproporphyria differing from porphyria variegata really occurred, and it was therefore excluded from the classification. Since then, Goldberg *et al.*[9] have described 10 new cases of hereditary coproporphyria with a summary of 20 other cases from the literature, and they conclude that this disease is different from porphyria variegata, characterized by a high excretion of coproporphyrin III in the urine and predominantly in the faeces. The condition was not just symptomless, but acute attacks could occur as in intermittent acute porphyria and porphyria variegata. Goldberg *et al.* considered coproporphyria as probably hereditary in nature and transmitted as a Mendelian-dominant character, and they considered that it was hepatic rather than erythropoietic in type. The term hereditary coproporphyria was first proposed by Berger and Goldberg in 1955.[10] Inherited coproporphyria has not been previously described in Southern Africa.

COPROPORPHYRIA IN A FAMILY GROUP FROM LOURENÇO MARQUES, MOZAMBIQUE

The propositus (IV-3) of the Mozambique branch of the family consulted one of us (G.D.) in May 1966 with a history that three months earlier, after becoming pregnant with her first baby and while on holiday, she developed severe abdominal pain and was given a number of drugs including chloroquin because malaria was suspected. She became very hysterical and emotionally disturbed and was

admitted to hospital, where it was noticed that her urine was dark red in colour. The urine fluoresced in ultraviolet light and a diagnosis of acute porphyria was made. The patient already knew that there was porphyria in the family because one of her uncles had died in the Johannesburg Hospital 2 years earlier, and just before his death a diagnosis of acute porphyria had been made. She also reported that one of her aunts had died at the age of 23 years from what had been diagnosed as biliary fever because she had passed a dark reddish urine, and an uncle had died at the age of 35 years, although in the case of the uncle a diagnosis of suspected cancer had been made. He also had passed a very dark red urine for some days before his death.

In May 1966 the propositus reported that she was still having abdominal pain but that since she had been taking chlorpromazine 25 mg. 3 times a day the pain had been much less frequent and less severe. On examination she was anxious and tense but looked well. The Watson-Schwartz test was positive. Her urine darkened on standing in sunlight for 24 hours and it then gave a brilliant pink fluorescence in ultraviolet light. A fragment of stool, dissolved in a solvent of equal parts of amyl alcohol, glacial acetic acid and ether, also showed a brilliant pink fluorescence in ultraviolet light. When hydrochloric acid (1/N solution) was shaken up with the mixture the fluorescent pink colour passed down into the acid solution, showing that the pink fluorescence was due to porphyrin and not to chlorophyll.[11]

Quantitative studies of the porphobilinogen and porphyrin in the urine and stool of this patient and of the other members of the family were carried out at the South African Institute for Medical Research, Johannesburg, using the methods of Rimington and Holti (S.K.).[12] When the propositus of this family was first seen, quantitative analysis of the porphobilinogen in the urine confirmed that it was raised to 14·5 μg./ml. (normal = < 2 mg./day). Her urine coproporphyrin was greatly increased to 2,032 μg./litre (normal = 50 - 200 μg./day), and the uroporphyrin was also high but not as high as the coproporphyrin, 449 μg./litre (normal = 5 - 30 μg./day). Her stool coproporphyrin was 841 μg. and the protoporphyrin was 187 μg./G dry weight (normal = 0 - 36 and 0 - 113 μg./G dry weight, respectively). The increase of coproporphyrin relative to the uroporphyrin in the urine and relative to the protoporphyrin in the stool was so marked that it was suspected that the patient had inherited a disorder different from porphyria variegata, in which the protoporphyrin is usually in the same general range as the coproporphyrin.

Rimington[13] has recently described a porphyrin-peptide conjugate which he has named 'X porphyrin'. This porphyrin is excreted in greatly increased amounts in the stool of patients with porphyria variegata. It is also excreted in greatly increased amounts in the urine during attacks of acute porphyria variegata. There is no, or only a moderate, increase in the faecal excretion of X porphyrin in acute intermittent porphyria studied during remission.

Specimens of stool from 3 members of this family who had inherited coproporphyria were studied by Rimington. He confirmed the very high excretion of coproporphyrin and to a lesser extent protoporphyrin, but found no increase in the porphyrin-peptide conjugate, X porphyrin.[13]

The husband of the propositus was most cooperative with this study, and with his help a family tree was drawn up (Fig. 1). Every effort was then made to interview all the living members of the family and to obtain the case records of those who had died. The propositus of this family group, IV-3 in the family tree, was advised to take no other sedatives except chlorpromazine 25 mg. 3 times a day. This treatment suited her well, and over a period of 2 months her abdominal pains ceased and the Watson-Schwartz test became negative.

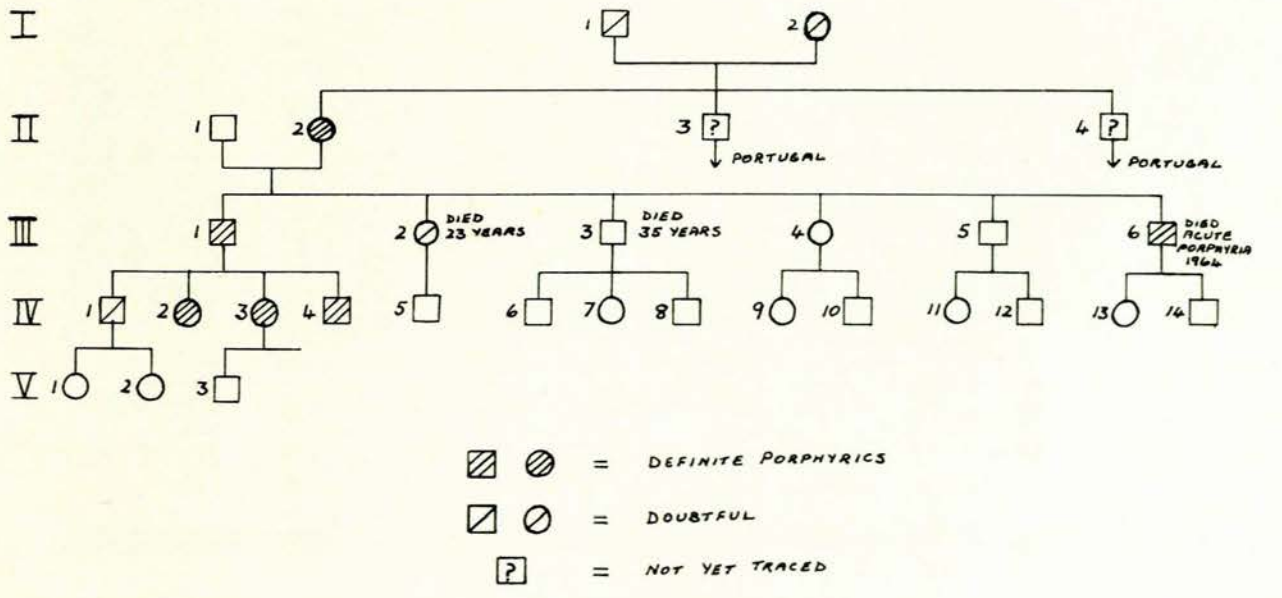

Fig. 1. See text.

One of us (P.L.) visited Mozambique on a number of occasions and interviewed the other members of the family, and specimens of urine and stool were screened in Port Elizabeth (G.D.) and examined quantitatively in Johannesburg (S.K.). The brother (IV-4) and sister (IV-2) of the propositus also had greatly increased coproporphyrin in the urine and stool. Another brother (IV-1) had increased porphyrin in his urine on one occasion, but a quantitative analysis was not carried out, and in subsequent specimens there was only a slight increase in the coproporphyrin. He may also have inherited coproporphyria. The results of the screening and quantitative analysis of the urine and stool of all the members of the family living in South Africa are shown in Table I. Stool coproporphyrin from the grandmother of the propositus was identified chromatographically as type III.

It will be noted that hereditary coproporphyria often causes no symptoms. The increase in coproporphyrin may be quite slight and the diagnosis may be difficult to make as in III-1, who undoubtedly has inherited coproporphyria because his mother, brother and children have. In 2 of the children under the age of 8 years in this family group who have a parent with coproporphyria (IV-13,14, V-1,2,3) there was no significant increase in coproporphyrin. It is probable that in coproporphyria as in porphyria variegata and intermittent acute porphyria the increase in the excretion of porphyrin or porphyrin precursors does not become clear until the age of puberty. In these 5 young children judgement as to whether or not they have inherited coproporphyria must be suspended until they are older and are reinvestigated.

Acute Coproporphyria

Apart from the propositus who made a good recovery from her attack of acute porphyria in 1966, one uncle and probably one aunt also died from acute porphyria. The uncle of the propositus, III-6, developed pain in his shoulders and chest in February 1964. He was treated for these symptoms and he then developed pain in the abdomen, with vomiting. A barium meal in hospital in Lourenço Marques showed only a small hiatus hernia, for which surgery was advised. After 2 days in hospital he complained of severe abdominal pain and started to pass dark urine. It was thought to be haematuria and he was referred to a urologist in Johannesburg. He collapsed in the urologist's room and was admitted to a nursing home. Pancreatitis was suspected and he was put onto gastric suction, intravenous therapy and barbiturate sedation. He was confused and restless, but appeared to improve after 3 days. His serum amylase was normal. He then developed weakness in the back muscles, and a physician was called to see him. It was noticed that the patient's urine became port-

TABLE I. COPROPORPHYRIA

No.	Age in 1966	Urine					Stool			Comment
		Screening (Dean)		Quantitative (Kramer)			Screening in UVL (Dean)	Quantitative (Kramer et al.) porphyrin		
		Watson-Schwartz	Porphyrin in UVL	PBG µg./ml.	Porphyrin					
					Copro µg./litre	Uro µg./litre		Copro	Proto	
Normal		Neg.	Neg.	<2	50–225	5–30	Neg.	0–36	0–113	
II– 1	78	Neg.	Neg.	2–10 doubtful	13·4	2·7	Neg.	18	31	Negative
II– 2	76	Neg.	++		108·6	28·0	+	625	24	Positive
III– 1	55	Neg.	++				+	50	64	Quiescent
		Neg.	Neg.	1·3	96	6·7	+–	41	37	Positive
III– 2	23*									Died aged 23
										? from acute porphyria
III– 3	35*									Died ? cancer, 1957
III– 4	42	Neg.	Neg.	3·8	58	16	Neg.	8	45	Negative
					Neg.	Neg.				
III– 5	35	Neg.	Neg.		78·7	9·5	Neg.	16	35	Negative
III– 6	30*	Pos.	Pos.		Up to 42,328	Up to 6,598	Pos.	2,246	673	Died acute porphyria Johannesburg 1964 (see full report)
IV– 1	31	Neg.	Pos.++	—	—	—	+	12	64	
				5·7	Neg.	Neg.		23	79	
IV– 2	27	Neg.	Pos.	0·63	1,357	64	Pos.	2,239	184	Kramer, Nov. '66
		Neg.	Pos.	—	1,040	240	Pos.	2,530	670	Barnes, Dec. '66
			Pos.	4·4	1,476	166	Pos.	2,429	539	Eales, Jan. '67 } Positive
			Pos.		2,368	111	Pos.	1,691	496	Kramer, Aug. '67
								342	175	Rimington
IV– 3	25	Pos.	+++Pos.	14·5	2,032	449	Pos.	1,466	114	Kramer, May '66
								841	187	Positive
		Neg.	Pos.		7,000	5,150		2,530	960	Barnes, May '66
IV– 4	25	Neg.	Pos.	3·15	1,167	59	Pos.	2,324	202	May '66
								1,491	176	Positive
IV– 5	26	Neg.	Neg.		16·7	Neg.	Neg.	16·9	20·1	Negative
IV– 6	18	Neg.	Neg.	0·63	84·7	23·9	Neg.	30·8	186	Negative
					66	10·6		17·8	33·0	
IV– 7	15	Neg.	Neg.	1·3	30·0	9·9	Neg.	34	127	Negative
								3·4	10·6	
IV– 8	13	Neg.	Neg.	Nil	2·9	12·0	Neg.	13	65	Negative
IV– 9	18	Neg.	Neg.	7·6	102	18	Neg.	3	10·4	Negative
IV–10	14	Neg.	Neg.	0	0	9·3	Neg.	3·3	21·5	Negative
IV–11	5	Neg.	Neg.	0	16·9	0	Neg.	9	9	Negative
IV–12	4	Neg.	Neg.		28·1	3·7	Neg.	8	10	Negative
IV–13	5	Neg.	Neg.	0	0	80	Neg.			
				0	51	6·4	Neg.	17·7	100	?
								4·4	97·6	–
IV–14	3	Neg.	Neg.	1·3	Nil	51·0	Neg.	17	92·0	?
					34·6	6·2		0·3	4	
V– 1	8	Neg.	Neg.	0	52·7	4·1	Neg.	45·5	105	?
								11·0	49	
V– 2	5	Neg.	Neg.	5·7	75·3	4·9	Neg.	9	40	?
V– 3	1	Neg.	Neg.	—	—	—	Neg.	2·8	1·0	?

*Age at death.

wine colour on standing, acute porphyria was diagnosed and barbiturates were immediately stopped. Nevertheless during the next few days the patient developed increasing weakness, particularly involving the back and abdominal muscles, so that he could not sit up and he found breathing difficult. The paralysis spread to his arms and became increasingly severe in spite of treatment with prednisone and intravenous cortisone, and he was therefore transferred to the Respiratory Unit at Johannesburg Hospital in a comatose condition. A tracheostomy was done and his respiration was assisted by means of a Bird respirator. The patient was maintained on an intravenous drip containing Solu-Cortef and Aramine. He was given 4 units of whole blood and chloramphenicol and penicillin. He developed a paralytic ileus and gastric suction was maintained. He died 7 days after admission.

The laboratory investigations that were carried out while this patient was in hospital are shown in Table II. It will be noticed that, as in acute porphyria variegata, there was a marked decrease in the blood and CSF chloride, although the blood sodium did not fall. His blood urea was raised.

An autopsy examination on this patient showed a widely dilated large bowel with multiple ulceration from the middle of the transverse colon to the rectum. One of the ulcers had perforated and had caused a local area of peritonitis. There was also evidence of terminal bronchopneumonia. In spite of the terminal changes found at autopsy, there is no doubt that this patient died from acute coproporphyria and had suffered an acute illness very similar to that which occurs in acute porphyria variegata. The significance of the very high coproporphyrin was not appreciated at the time.

An aunt of the propositus, III-2, died when she was 23 years old, probably from acute porphyria. She had had several attacks of abdominal pain and passed a red urine which was attributed to malaria and haematuria. Her first pregnancy was uneventful, but in the eighth month of her second pregnancy she had a slight fever and passed a very dark urine. She died in spite of intensive treatment for malaria. The diagnosis of blackwater fever was made because of the colour of her urine. Both IV-2 and IV-4 in the family group have also had attacks of severe abdominal pain in which they passed a dark urine. Some of their attacks were so severe that they were admitted to hospital.

One of the family, IV-2, consulted one of us (G.D.) because of pain in her face which was found to be due to an impacted wisdom tooth. The tooth was removed under gas-and-oxygen anaesthesia without undue difficulty, and after its removal the pain disappeared. Although there was a great increase in coproporphyrin in her urine and stool, the Watson-Schwartz test was negative for porphobilinogen. She made a good recovery.

Inheritance

The forbear of this Mozambique family with coproporphyria, II-2, is 76 years old, very fit and gives no history of attacks suggestive of acute porphyria although she has increased stool coproporphyrin. She has had 2 operations and probably had a thiopentone anaesthetic but nevertheless she made a good recovery. She was born in Portugal and she has a brother and sister living in Portugal who have children and grandchildren. Members of this family in Portugal may also have inherited coproporphyria and we are investigating these members of the family in cooperation with Prof. D. Soares and Drs A. and M. Carlos of Lisbon University.

Coproporphyria in this family is inherited from one parent only, from either the father or mother, and is inherited therefore as a non-sex-linked Mendelian-dominant characteristic. The high faecal excretion of porphyrin relative to the urine porphyrin in the quiescent phase suggests that the porphyrin originates in the liver and is excreted in the bile.

DISCUSSION

No member of this family group who inherited coproporphyria had an unduly sensitive exposed skin, for instance on the back of the hands; i.e. a skin that abraded and blistered easily. Adult White South Africans who have inherited porphyria variegata generally have a sensitive skin on the back of their hands that abrades easily if scratched with a fingernail. Many of those who inherit porphyria variegata suffer from sores and blisters on the exposed skin at least when their porphyrin excretion is high. It is notable that even those members of this family with coproporphyria who had a very high urinary and faecal excretion of porphyrin did not have the sensitive skin which would have been expected if they had inherited porphyria variegata.

Hereditary coproporphyria must be compared and contrasted with the two other known varieties of Mendelian-

TABLE II. ACUTE COPROPORPHYRIA: MALE, AGED 31 (III-6)*

	Blood						*CSF*		*Urinary porphyrin* µg./litre		*Stool porphyrin* µg./G dry wt.	
Date	*Urea* mg./100 ml. (10–32)	*Na* mEq. (133–144)	*Cl* mEq. (100–111)	*K* mEq. (3·6–4·6)	*Ca* mg./100 ml. (9–11)	*CO_2* mEq./litre (18–26)	*Cl* mg./100 ml. (700–750)	*Protein* mg./100 ml. (20–40)	*Copro* 50–225	*Uro* 5–30	*Copro* 0–36	*Proto* 5–30
11/3/64	128	131	71	4·5		18						
12/3/64	175	131	71	4·3		24						
13/3/64	121	129	87	3·6		24						
15/3/64	167	135	91	4·4		28						
16/3/64	120	139	94		9·4							
21/3/64				4·9								
25/3/64							650	49				
3/4/64	106	132	112	4·8		17	750	20				
7/4/64	99	138	105	3·8								
7-8/4/64									20,008	4,163	2,246	673
									42,328	6,598		
									24,684	5,148		
									24,684	4,706		

*Laboratory investigations carried out by Dr B. M. Bloomberg of Clinical Laboratories, Johannesburg, for Dr I. J. Grek, physician. Liver-function tests 25/3/64: Bilirubin 0·2 mg., thymol turbidity 1 unit, alkaline phosphatase 15·5 units. Haemoglobin 11/3/64: 17·8 G/100 ml. 4/4/64: 9·7 G/100 ml. Leucocytes 20,000.

dominant hepatic porphyria—acute intermittent porphyria and porphyria variegata. The striking clinical difference is the presence of skin lesions in some members of the family in porphyria variegata. This is not present in acute intermittent porphyria, and photosensitivity has been described in only one patient with hereditary coproporphyria, and this was provoked by hepatic insufficiency.[14]

In all 3 types acute episodes may be precipitated by certain drugs, particularly barbiturates, and in the acute attack large amounts of porphobilinogen and delta-aminolaevulinic acid will be passed in the urine with increased coproporphyrins in hereditary coproporphyria. In remission the Watson-Schwartz test for porphobilinogen is usually positive in intermittent acute porphyria and usually negative in porphyria variegata and coproporphyria. In remission in hereditary coproporphyria there may be some increased excretion of porphyrin, particularly coproporphyrin, in the urine.

In acute intermittent porphyria, stool porphyrins are normal, whereas in hereditary coproporphyria there is a striking increase in coproporphyrins relative to protoporphyrins, and in porphyria variegata there is increased excretion of both copro- and protoporphyrins.

Now that we have considerable knowledge of the biochemical differences in 3 types of similar, but different, Mendelian-dominant hepatic porphyria, it should be possible to work out where in the chain of porphyrin metabolism the inherited abnormality in each type takes place.

SUMMARY

A family with inherited coproporphyria from Mozambique, Southern Africa, is described. On superficial observation coproporphyria is very similar to porphyria variegata, except that no skin lesions occurred in members of this family. The symptoms, signs and biochemistry of acute coproporphyria are very similar to those of acute porphyria variegata, except for the very high level of coproporphyrin in the urine and stool in acute coproporphyria. Coproporphyria should be included in our classification of the porphyrias as an autosomal Mendelian-dominant hepatic porphyria.

A comparative study of patients with the 3 types of autosomal-dominant hepatic porphyria, perhaps with the aid of radioactive tagging of porphyrin precursors, should make it possible to elucidate the pathways of porphyrin metabolism.

We wish to thank this family for their wholehearted cooperation with the study; Mr J. Q. de Oliveira, Dr Mercial Ribeiro, Dr Afonso Paes, and the staff of the South African Consulate-General of Lourenço Marques who went to great trouble to obtain for us full family and medical histories; Prof. C. Rimington of University College Hospital, London, and Prof. A. Goldberg of the Department of Medicine, Glasgow, for advice and assistance in carrying out estimations of porphyrin, including X porphyrin, on specimens from 3 members of this family who had inherited coproporphyria; and Prof. L. Eales and his staff of the Medical School, University of Cape Town, Dr H. Barnes, formerly of the SAIMR, Johannesburg, and Mrs E. Viljoen, who assisted us with biochemical studies. We should also like to thank the Director of the SAIMR, Johannesburg, Dr I. J. Grek, consultant physician to Johannesburg Hospital, and Dr B. M. Bloomberg, of Johannesburg, for details about the member of this family who had acute porphyria in 1964.

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REFERENCES

1. Conference Discussion (1963): S. Afr. J. Lab. Clin. Med., **9**, 302.
2. Waldenström, J. (1937): Acta med. scand., suppl. 82.
3. Watson, C. J. and Schwartz, S. (1941): Proc. Soc. Exp. Biol. (N.Y.), **47**, 393.
4. Dean, G. (1963): *The Porphyrias : A Story of Inheritance and Environment*. London: Pitman.
5. Barnes, H. D. (1955): S. Afr. Med. J., **29**, 781.
6. Dean, G. (1961): *Ibid.*, **35**, 509.
7. Fischer, H., Hilmer, H., Lindner, F. and Putzer, B. (1925): Hoppe-Seylers Z. physiol. Chem., **150**, 44.
8. Magnus, I. A., Jarrett, A., Prankerd, T. A. J. and Rimington, C. (1961): Lancet, **2**, 448.
9. Goldberg, A., Rimington, C. and Lochhead, A. C. (1967): *Ibid.*, **1**, 632.
10. Berger, H. and Goldberg, A. (1955): Brit. Med. J., **2**, 85.
11. Dean, G. (1960): S. Afr. Med. J., **34**, 745.
12. Rimington, C. (1961): The Association of Clinical Pathologists Broadsheet No. 36 (new series).
13. *Idem*: Personal communication.
14. Langhof, H., Franken, E. F. and Kluge, K. (1965): Hautarzt, **16**, 101.