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Relation of Methemoglobin to the Cyanosis Observed After Sulfanilamide Administration.

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Two explanations have been offered for the cyanosis often noted after sulfanilamide administration. The first is that the drug causes formation of methemoglobin, or (secondarily, because of the presence of sulphur) sulfhemoglobin.[1, 2] The second is that a black[3] or blue pigment[4] derived from sulfanilamide, occurs in the blood and produces cyanosis. We have confirmed Ottenberg and Fox's observation[4] that colorless sulfanilamide solutions are changed to a bluish purple when exposed to ultraviolet light. The results of the present study reveal, however, that a pigment derived from sulfanilamide is not directly responsible for the cyanosis. We are now convinced that the cyanosis due to sulfanilamide is caused in all instances by methemoglobin (rarely sulfhemoglobin). In order to detect methemoglobin in every case it has been necessary to employ a sufficient concentration of laked blood (1:5, tube thickness 2 cm; Zeiss grating spectrometer). With more dilute solutions we have often failed to detect appreciable concentrations of methemoglobin.

The concentration of methemoglobin in the blood has been measured by one or both of two methods in a series of 26 determinations. The first method was a spectrocolorimetric procedure such as used previously for measuring the concentration of porphyrin.[5] Blood laked with distilled water in varying dilutions of from 1:10 to 1:30 (depending upon the relative concentration of methemoglobin), was compared with a 1:100 dilution of the same blood in distilled water, in which all of the hemoglobin was converted to methemoglobin by addition of $K_3Fe(CN)_6$. (2-3 mg to 100 cc). The second method was spectrophotometric, such as employed by Heilmeyer;[6] certain modifications will be described in

1 Paton, J. P. J., and Eaton, J. C., *Lancet*, 1937, **1**, 1159.

2 Hartmann, A. F., Perley, A. M., and Barnett, H. L., *J. Clin. Invest.*, 1938, **17**, 699.

3 Marshall, E. K., Jr., and Walzl, E. M., *Bull. Johns Hopkins* Hosp., 1937, **61**, 140.

4 Ottenberg, R., and Fox, C. L., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 479.

5 Watson, C. J., *J. Clin. Invest.*, 1937, **16**, 383.

6 Heilmeyer, L., *Medizinische Spektrophotometrie*, Jena, G. Fischer, 1933, p. 103.

TABLE I.

Case No.	Cyanosis	Spectroscopic detection of Methemoglobin band (1:5 dilution)	% of Methemoglobin with relation to total Hb.		Free blood sulfanilamide in mg %
			Spectrocolorimeter	Spectrophotometer	
1	+++	+			6.8
2	++++	+			7
3	+++	+	7.3		5
4	++	+			4.9
5	++	+			17.5
6 (12-17)	+++	+	2.5		
(12-18)	+++	+	8.0		20.8
(12-19)	+++	+	13.1		
(12-20)	+++	+	8.5	7.8	18.8
(12-21)	++	+	5.0		15.9
7	++	+	8.5	9.5	17.5
8 (12-21)	++++	+	30.9		9
(12-21)*	0*	0			
(12-30)†	++++†	+	30.3		
9	+++	+	14.2	13.3	7
10 (2-11)	++	+	10.0	12.3	9.6
(2-11)*	0	0		0.5	
11 (1-26)	+++	+	24.0	18.5	9.1
(1-26)*	0	0			
(1-27)†	++	+		13.4	6.1
12	+++	+	18.0	21.5	8.7
13	++	+	8.5	11.3	13
14 (3-3)	++++	+	38.4	40.0	6.4
(3-3)*	0	0			
(3-4)†	++++				
15	0	0		1.0	13

* 30 minutes after intravenous injection of 1% methylene blue solution (8-20 cc).

†After resumption or continuation of the drug.

detail elsewhere. The results of the study are shown in Table I.

These results confirm the conclusions of Hartman and his associates,[2] as well as the recent findings of Wendel[7] that methemoglobin (or sulfhemoglobin) is the cause of sulfanilamide-induced cyanosis, and that methylene blue, given intravenously, rapidly abolishes the methemoglobinemia. We have seen but one instance of sulfhemoglobinemia, and in this case, methylene blue had no effect. This patient had been given sulfanilamide because of peritonitis incident to carcinoma of the colon, bowel obstruction and perforation.

It should be emphasized that the spectral distribution curves of the bloods examined for methemoglobin with the spectrophotometer, failed to reveal the presence of any other pigment.

[7] Wendel, W. B., *J. Clin. Invest.*, 1939, **18**, 179.