

close to the vertical position as shown in the diagram as otherwise the flaps will be opened by gravity between respirations allowing significant leaks. Small springs to close the flaps might eliminate this danger. The valve should be stored in the vertical position when not in use. The tube (B) with a 45° bend, inserted into the stopper of the mask, is used when the

dog is supine with head tilted 45° upward. Modification of this bend permits use with the animal in any desired position. Modification of the diameter and bend of (B) and attachment to a suitable mask permits use on man. No significant resistance to respiration develops with these valves even during exercise or CO₂ inhalation.

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Effect of Salicylate on Plasma Fibrinogen and Sedimentation Rate in Rheumatic and Non-Rheumatic Patients.*

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Despite the long-standing use of salicylates in the management of rheumatic fever, considerable uncertainty still exists with regard to their efficacy and to their mode of action in this disease. While some observers believe that their clinical effect may be ascribed entirely to the analgesic and antipyretic action,¹ others have assumed a specific inflammation-suppressant effect of these drugs in rheumatic fever. Studies which indicated a more rapid return to normal of the sedimentation rate in rheumatic patients receiving large doses of salicylates were interpreted as supporting evidence for this view, under the assumption that the sedimentation rate represented an index of inflammatory activity.² A specific influence of the drug on the sedimentation rate apart from its assumed action on the inflammation is also suggested by the observation that the sedimentation rate may increase promptly on discontinuance of salicylate therapy.³

Present evidence indicates that the sedimentation rate of the erythrocytes is mainly

dependent on the concentration and distribution of the various fractions of the plasma proteins.⁴ Fibrinogen exerts the greatest accelerating action. A close relationship between the sedimentation rate and the level of fibrinogen has been demonstrated by several observers in various experimental conditions and diseases, among them rheumatic fever.⁵ Fibrinogen is generally believed to be formed solely in the liver.⁶ In view of these facts it appears possible that the effect of salicylates on the sedimentation rate of rheumatic patients is due to an inhibition of the formation of fibrinogen by the liver. That salicylates may affect liver function is also suggested by the observation that they may cause significant reduction in the plasma prothrombin in animals and in man.⁷ One would not expect such

⁴ Fåhræus, R., *Physiol. Rev.*, 1929, **9**, 241; Westergren, A., Theorell, H., and Widstroem, S., *Z. ges. Exp. Med.*, 1931, **75**, 668; Bendien, W. M., Neuberg, J., and Snapper, I., *Bioch. Z.*, 1932, **247**, 306; Grey, S. J., and Mitchell, E. B., *Proc. Soc. Exp. Biol. and Med.*, 1942, **51**, 403.

⁵ Ernstene, A. C., *Am. J. Med. Sc.*, 1930, **180**, 12; Gilligan, D. R., and Ernstene, A. C., *Am. J. Med. Sc.*, 1934, **187**, 552; Ham, T. H., and Curtis, F. C., *Medicine*, 1938, **17**, 447.

⁶ Madden, S. C., and Whipple, G. H., *Physiol. Rev.*, 1940, **20**, 194.

⁷ Link, K. P., Overman, R. S., Sullivan, W. R., Huebner, C. F., and Scheel, L. D., *J. Biol. Chem.*,

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¹ Hanzlik, P. J., *Medicine*, 1926, **5**, 197.

² Coburn, A. F., *Bull. Johns Hopkins Hosp.*, 1943, **73**, 435.

³ Liehty, J. A., and Hooker, S. P., *Proc. Soc. Exp. Biol. and Med.*, 1941, **48**, 69.

TABLE I.
Changes in Plasma Fibrinogen and Sedimentation Rate Following Salicylate Therapy.

Case No.	Diagnosis	Age, yrs	Dosage, g/kg/day	Time, relative to medication	Plasma fibrinogen, mg/100 cc	Sedimentation rate	
						uncorrected, mm/min.	corrected, mm/min.
1	Nephrosis	11	0	before	951	3.63	1.96
			0.13	2 days	857	3.07	1.80
			0.13	5 "	676	2.86	1.64
			0.13	10 "	534	2.35	1.33
			0.13	14 "	468	2.26	1.42
			0	8 " after	535	2.65	1.90
2	"	7	0	20 " "	764	3.09	2.00
			0	before	924	3.72	2.18
			0.15	16 days	652	3.00	1.88
3	"	8	0	8 " after	794	4.22	2.14
			0	before	653	2.20	2.00
			0.11	9 days	415	1.70	1.38
			0.11	16 "	184	1.27	1.02
4	Chron. staph. osteomyelitis	6	0	7 " after	479	1.55	1.33
			0	before	628	2.81	1.68
			0.09	7 days	360	2.52	1.48
			0	7 " after	690	3.15	1.83
5	" " "	3	0	before	501	1.64	1.04
			0.11	7 days	220	1.06	0.65
			0	14 " after	598	1.06	0.68
6	Brain abscess	14	0	before	858	4.64	1.77
			0.15	4 days	780	2.49	1.40
			0.15	13 "	583	1.24	1.18
7	Rheum. fever	2	0	before	843	2.50	1.35
			0.20	7 days	608	1.34	0.72
			0.20	20 "	376	0.73	0.45
8	" "	12	0	before	858	2.71	1.60
			0.13	5 days	589	2.26	1.42
			0.13	20 "	404	0.52	0.28
			0	45 " after	631	0.97	0.78
9	" "	5	0	before	622	1.86	1.18
			0.17	7 days	552	0.80	0.36
			0.17	29 "	388	0.19	0.12
10	" "	7	0	before	614	2.83	1.74
			0.13	14 days	548	2.19	1.18
			0	12 " after	673	2.32	1.50
11	Nephrosis	7	0	before	785	6.50	2.10
			0.14	7 days	808	6.74	2.12
			0	7 " after	940	7.57	2.57
12	Brain abscess	8	0	before	726	1.16	0.68
			0.13	12 days	746	1.34	0.74
13	Rheumatoid arthritis	11	0	before	626	2.41	1.70
				10 days	640	2.81	1.94
				12 " after	740	4.22	2.44
14	Pericarditis und. etiol.	2	0	before	472	1.26	0.72
			0.18	6 days	506	1.16	0.63
15	Rheum. fever	14	0	before	619	—	—
			0.13	9 days	592	0.80	0.66
			0.13	16 "	614	1.13	0.80

an effect of the salicylates to be limited to rheumatic patients alone; decreases in the

1943, **147**, 463; Rapoport, S., Wing, M., and Guest, G. M., *Proc. Soc. Exp. Biol. and Med.*, 1943, **53**, 40; Meyer, O. O., and Howard, B., *Proc. Soc. Exp. Biol. and Med.*, 1943, **53**, 234; Shapiro, S., Redish, M. H., and Campbell, H. A., *Proc. Soc. Exp. Biol. and Med.*, 1943, **53**, 251.

plasma fibrinogen and in the sedimentation rate following salicylate medication should be demonstrable in other patients with elevated sedimentation rates, who do not suffer from rheumatic fever. In the present study parallel determinations of the sedimentation rate and of plasma fibrinogen were carried out before, during, and after courses of salicylate adminis-

tration in patients suffering from various chronic disorders in which the sedimentation rate is elevated.

Material and Methods. Fifteen patients with elevated sedimentation rates, varying in age from 2 to 14 years, were chosen for this study. Eight displayed some manifestations of rheumatic fever, 4 were suffering from lipoid nephrosis, and 3 from chronic osteomyelitis. The subjects received daily 0.09-0.22 g per kg of body weight of acetyl-salicylic acid combined with an equal amount of sodium bicarbonate for a period of 7 to 29 days. Blood samples for the determination of the sedimentation rate and of the plasma fibrinogen were obtained before, during, and after the period of medication at varying intervals of time, usually 3 to 5 days. Most subjects tolerated the drug well, except for one patient with nephrosis who developed hypoprothrombinemia and hematuria; shortly after discontinuance of salicylate medication the hematuria ceased and the prothrombin returned to normal.

The sedimentation rate was determined by the method of Rourke and Ernstene⁸ using heparinized blood with values corrected for the packed volume of cells. Fibrinogen was determined as fibrin, following essentially the procedure of Cullen and Van Slyke.⁹

Results. Ten of the patients, whose data are summarized in Table I, exhibited significant reduction in the fibrinogen level of their plasma during periods of salicylate medication.

⁸ Rourke, M. D., and Ernstene, A. C., *J. Clin. Invest.*, 1930, **8**, 545.

⁹ Cullen, G. E., and Van Slyke, D. D., *J. Biol. Chem.*, 1920, **41**, 587.

In all instances the sedimentation rate of the erythrocytes was also reduced, but the extent of the decrease varied considerably. In the other 5 patients, in whom the plasma fibrinogen did not decrease, no important changes were observed in the sedimentation rate. Several striking discrepancies between the two indices, demonstrated particularly in Cases 3, 5, and 8 in Table I, would indicate that other factors besides fibrinogen were operative in determining the sedimentation rate. It well may be that the effect of the salicylates on the distribution of plasma protein, and with it on the sedimentation rate, is not limited to fibrinogen alone, although determination of albumin and globulin by the conventional Howe method in several of the samples did not indicate significant change. The data on Cases 1 to 6 would indicate that salicylates may lower the plasma fibrinogen and the sedimentation rate in conditions unrelated to the rheumatic disorder. Such findings justify the assumption that salicylates exert an unspecific action on the liver, and indirectly support the contention of those observers who believe that salicylates do not have a specific anti-rheumatic action. However, it is of course conceivable that changes in the distribution of plasma protein produced by salicylates may in some manner influence favorably the course of rheumatic inflammation.

Summary. In 10 of 15 patients with elevated sedimentation rates, suffering from non-rheumatic and rheumatic disorders, the sedimentation rate and concentration of fibrinogen decreased following salicylate therapy. It is suggested that the change in the fibrinogen may represent an effect of salicylate on the liver.