tamine is quite similar to death from anaphylactic shock. But one would have expected a reduction in the number of histamine deaths if the compounds under study produced merely a non-specific increase in resistance. Furthermore, no correlation could be found between anti-pyretic and anti-anaphylactic activity. Also, a different type of analgesic, codeine, and the hypnotic compound, nembutal, were ineffective. However, it is impossible to state with certainty that pharmacological or chemical effects other than interference with the immune reaction may not be important.

The "negative" results obtained with the other compounds indicate only that they are not as effective as salicylate and aminopyrine. One cannot be sure that more tests with this or other methods will find them devoid of activity. The results with neocinchophen may have been influenced by difficulty in administration and absorption. However, because this compound produced a definite anti-pyretic effect, it appears certain that a fairly large percentage of the dose must have been absorbed.

The failure of sodium gentisate to prevent anaphylactic shock is interesting because of the suggestion of Meyer and Ragan(18) that salicylate acts in rheumatic fever only after conversion to gentisate.

It is hoped that further studies with salicylates, aminopyrine, and related compounds will elucidate the site and mechanism of action of the inhibitory effect. Their influence on other protein, as well as non-protein, sensitizations should be of interest. A simpler technic for screening compounds for activity is desirable because the present method is too cumbersome and expensive.

Summary. 1. Oral administration of salicylates and aminopyrine in rabbits decreased the incidence of death from anaphylactic shock. 2. A number of compounds closely related, chemically or pharmacologically, did not produce a similar inhibitory effect. 3. The mechanism of action is not antihistaminic, nor does it appear to be related to characteristic pharmacological effects, *e.g.* antipyresis. It may represent a direct effect on the specific combination of antigen and antibody.

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Effect of Metal-Combining Globulin (Fraction IV-7) in Severe Mediterranean Anemia.* (17871)

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Iron is transported in the serum only in attachment to a B_1-globulin, called the "metal-combining globulin", which resides in Fraction IV-7 of the plasma(1). Except under certain conditions this globulin is not completely saturated with iron, and the excess in reserve is measurable. The determination of the serum iron level measures the degree of saturation of this protein. The method of Rath and Finch(2) employed for the determination

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1. Surgenor, D. M., Koechlin, B. A., and Strong, L. E., *J. Clin. Invest.*, 1949, v28, 73.

2. Rath, C. E., and Finch, C. A., *J. Clin. Invest.*, 1949, v28, 79.

TABLE I.
Effect of Injection of Metal-Combining Globulin (Fraction IV-7) in Severe Mediterranean Anemia.

Patient	Age yr.	Fraction IV-7 inj., g	Interval after infusion hr	Interval after infusion min.	Serum Fe content, γ/100 ml	Latent Fe binding capacity serum	Hemoglobin, g	Hematocrit, %
S.	11½	4		0	134.1	0	6.3	24.4
				5	142.7	75	6.6	20.4
				20	141.1	150	6.6	20.2
			1	5	193.3	0	8.2	21.0
			2	5	190.7	50	6.9	20.6
			4	15	169.0	0	7.3	22.3
			24		224.0	100	7.1	22.5
			48		204.6	0	7.3	20.5
				Splenectomy* 12/1/49				
		5		0	227.8	0		
				5	210.9	120	12.0	36.
				35	217.2	150	13.1	40.
			1	5	248.7	167	13.6	41.
			2	5	212.4	155	13.3	42.5
			3	5	240.8	0	13.1	39.
			5	5	229.3	0	13.1	40.5
I.	15	5		0	291.4	0	8.0	26.
				30	305.1	0	8.3	30.
			1		334.1	0	8.7	26.5
			2		327.0	0	8.6	27.3
			4		322.0	0	8.5	27.0
A.V.	12	5		0	167.1	0	8.0	26.5
				15	243.9	100	6.2	22.0
				45	211.0	50	6.9	26.0
			1	15	244.2	0	7.4	26.0
			2	15	237.8	0	7.5	24.5
			4	15	226.4	0	7.0	23.5
A.	13	10		0	207.7	0	8.0	24.5
				8	283.1	150	6.2	20.2
				33	402.8	0	7.4	24.0
			1	38	391.6	0	7.0	22.3
			2	38	341.0	0	6.4	21.0
			5	15	328.9	0	7.4	23.0
			24		195.5	0	7.7	26.5

* Between 11/25 and 11/29/49, 5 transfusions, totaling 1,250 cc of blood were given. This accounts in large measure for the elevated blood levels of the post-splenectomy period.

of the reserve, latent or unbound iron capacity of the serum depends on the addition of known quantities of iron to measured amounts of serum with the formation of a distinctive color-complex when iron is linked to the metal-combining globulin. The total iron binding capacity is the sum of the two values (serum iron level and latent iron-binding capacity). In a previous study(3) the blood of children with severe Mediterranean anemia was found to have an elevated serum iron and no latent or reserve iron-binding capacity. In normal children and adults, by contrast, the iron-binding capacity is quantitatively higher and the serum iron levels comprise approximately one-third of the total capacity. Comparable changes were noted in children with spherocytic anemia and sickle cell anemia. The marked reduction in total iron-binding capacity in these related hemolytic anemias suggested a congenital and possible transmissable deficiency of the metal-combining protein. With the availability of this plasma component in purified form†, tests were made to determine

3. Smith, C. H., Sisson, T. R. C., Floyd, W. H., Jr., and Siegal, S., *Pediatrics*, 1950, v5, 799.

† For furnishing this material and for many helpful suggestions, we are indebted to Dr. Douglas M. Surgenor, Harvard Medical School, Boston, Mass.

whether the serum iron and iron-binding capacity could be altered by its administration. Four children with the severe form of Mediterranean anemia were the subjects of the present investigation. Their blood was characterized by an elevated serum iron and no capacity to further bind iron. In one of these patients (S) the effect of administering the Fraction IV-7, containing the metal-combining globulin, was observed before and after splenectomy. Immediately preceding and at intervals following the intravenous injection of Fraction IV-7 over a period of ½ to 1 hour in amounts varying from 4 to 10 g in 500 cc normal sodium chloride solution, blood samples were withdrawn for analysis as noted in Table I. Serum iron levels, the capacity of the serum to bind iron, hematocrit and hemoglobin were determined on each sample in duplicate. The methods for the first 3 measurements have been previously described(2,4,5). Hemoglobin was determined by the method of Evelyn(6). The measurement of the serum iron-binding capacity(2) depends on optical density; full capacity to combine with iron is indicated by no further changes in density except in later phases due to the factor of dilution. The end point is marked by the salmon-pink color produced when increasing amounts of iron are added to the metal-combining protein.

Results. In each subject the serum iron level rose, most strikingly in patient D who had received 10 g of the fraction. The magnitude and duration of the post-injection rise differed in each subject. In general, the use of 5 g and more of Fraction IV-7 produced a rise sustained for 3 to 5 hours. In patient S the level remained elevated for 24 hours after the administration of 4 g of the fraction, whereas after 10 g in patient D there was a return to the lower pre-injection level within the same period. The varied curves probably reflect the extreme individuality of each case of Mediterranean anemia in regard to the degree of hemolysis and resulting iron storage. The consistent increase in serum iron following the injection of the metal-combining globulin suggests the release of iron from the tissues to the blood. These observations are in contrast with changes occurring in chronic infection. In the latter, Cartwright and Wintrobe(7) noted that after the injection of the globulin the temporary restoration of the total iron-binding capacity to normal from initially reduced levels was not accompanied by mobilization of iron from storage depots.

In subject S, both before and after splenectomy, in V, and in D, the injection of Fraction IV-7 produced a transitory latent capacity to bind iron in the serum. The effect was prolonged in S after splenectomy. The fleeting, ill-sustained appearance and reappearance of a latent iron-binding capacity in S before splenectomy cannot be correlated with serum iron levels, and no explanation for it can be assigned at this time. Irregularity in the latent iron-binding capacity, as compared with the consistent alterations in serum iron levels, may be due either to physiologic changes or to errors inherent in the method. No latent capacity to bind iron was induced in subject C, whose initial serum iron level was higher than all the rest.‡ The greater magnitude of serum iron and iron-binding capacity in S following splenectomy may be attributed in part to the injection of 5 g of the fraction as compared with 4 g prior to the operation. While subject C with a high initial serum iron value, had a splenectomy in early childhood, the possible effect of the removal of the spleen on serum iron values awaits confirmation with more extended experience. The effect of administering Fraction IV-7 to children without anemia is under

4. Kitzes, G., Elvehjem, C. A., and Schuette, H. A., *J. Biol. Chem.*, 1944, v155, 653.

5. Smith, C. H., *Am. J. Dis. Child.*, 1948, v75, 505.

6. Evelyn, K. A., *J. Biol. Chem.*, 1936, v115, 63.

7. Cartwright, G. E., and Wintrobe, M. M., *J. Clin. Invest.*, 1949, v28, 86.

‡ Since this paper was written, the administration of 20 g of Fraction IV-7 to this subject has resulted in a greater elevation of the serum iron level and the brief appearance of a latent iron-binding capacity with maximum values of 617 γ and 167 γ/100 cc of serum respectively. Treatment with increased quantities of the fraction is being investigated in other cases.

investigation.

Comparable results were obtained in a child with severe sickle cell anemia. Upon the administration of 5 g of Fraction IV-7, the serum iron rose from 245γ/100 cc of serum to a maximum of 310 γ in approximately 4 hours. No latent iron-binding capacity appeared.

Whether Fraction IV-7 furnishes a factor required for hemoglobin synthesis and red cell formation could not be established with the amounts of this material employed in the present study and within the short observation periods. Table I, which provides figures for 24 hour periods of observation, reveals entirely insignificant deviations of the hemoglobin and hematocrit values from the pre-injection levels.

Conclusion. The administration of Fraction IV-7 of plasma to 4 patients with severe Mediterranean anemia resulted in a consistent rise in serum iron values in all, and in a transitory appearance of a latent capacity to further bind iron in 3 of the 4 subjects. These observations suggest the release of iron from the tissues to the blood when additional metal-combining globulin is supplied in this disease. Further studies are in progress to explore the clinical value of Fraction IV-7 both in Mediterranean anemia and exogenous hemochromatosis associated with multiple transfusions.

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Absorption and Excretion of Terramycin in Humans: Comparison with Aureomycin and Chloramphenicol.* (17872)

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Terramycin is a recently discovered antimicrobial compound which is produced by a species of Streptomyces(1). This drug has been found to be active against a number of bacterial species *in vitro* and to suppress experimental infections in mice(2). Clinical investigation of terramycin is now in progress (3). Studies in laboratory animals have indicated that terramycin, like aureomycin and chloramphenicol, is well absorbed following oral administration(4). It seemed desirable, therefore, to make a study of the absorption, distribution, and excretion of terramycin following its administration to humans and to compare the data with those obtained following the administration of aureomycin or chloramphenicol (Chloromycetin®). In addition, the serum concentrations of these drugs attained in patients under treatment with various dosage regimens have been determined.

Materials and methods. Preparations of drug. Terramycin‡ was supplied as the amphoteric base in 250 mg capsules and in 2.5 g vials for aqueous suspension and as the hydrochloride in 250 mg capsules and com-

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† Postdoctorate Research Fellow, National Institutes of Health, U. S. Public Health Service.

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‡ Supplied by Charles Pfizer and Co., Brooklyn, N.Y.