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Rutin in Histamine Shock.*

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The vitamin P substances are a closely related group of compounds which were introduced by Armentano and Szent-Gyorgyi[1] and co-workers as capillary stabilizers. The increased capillary fragility in allergic states led to the study of their effects in allergic diseases and histamine shock. The published findings are contradictory. Jersild,[2] who presented the first of the anti-allergic reports, claimed dramatic improvement when a patient with severe Henoch-Schonlein's purpura was given vitamin P. More recently, Davis,[3] without giving details, stated that vitamin P had no effect on this disease. Kugelmass[4] reported two cases of allergic purpura which responded favourably to vitamin P and Madison and Pohle,[5] in a preliminary note, have indicated that rutin has some beneficial effect in this disease. Rappaport and Klein[6] claimed to have reversed by means of calcium eriodictate, the abnormal capillary fragility seen in allergic children. Unfortunately they failed to mention the effects, if any, on the associated clinical allergic manifestations. In the guinea pig, protection against serum anaphylaxis by hesperedin, has been claimed by Hiramatsu[7] and confirmed by Raiman, Later and Necheles,[8] using rutin. In a report of preliminary studies, Wilson, Mortarotti and De Eds,[9] employing rutin, could find no such antihistamine effect in the guinea pig, when an M.L.D. of histamine was used. Wilson *et al.*[9] thought that rutin did exert an antihistamine effect when the dose of histamine was L.D. 50. However they had pretreated their animals with a vitamin P-free diet. As Parrot and Richet[10] have shown, this diet renders guinea pigs more susceptible to histamine and a dose of histamine which is L.D.50 for normal guinea pigs, may become L.D.100 for P-deficient animals. The effect of rutin therefore may have been the restoration of histamine sensitivity to normal and the findings cannot be interpreted with respect to normal animals. This information became available to Wilson *et al.* after their experiments were completed. Finally, Ambrose and De Eds[11] have shown that intravenous rutin delays the appearance of intravenous trypan blue in histamine induced skin wheals.

The doses of rutin administered by Wilson *et al.*[9] varied up to 10 mg and Raiman *et al.*[8] 2 mg. In the present experiments, the possible anti-histamine effects of large doses of rutin‡ were studied in rabbits. The rutin was given orally, in tablets, or parenterally in propylene glycol solution or emulsion. In one series, repeated injections of rutin preceded the histamine. The M.L.D. for intravenous histamine dihydrochloride§ was found

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‡ Furnished by the Charles E. Frosst & Co., courtesy Dr. E. Lozinski.

§ Furnished by the Hoffman La-Roche Co., courtesy Mr. P. Blanc.

TABLE I.
Effect of Single Injections of Rutin on Histamine Shock.

No.	Wt, lb	Sex	Rutin, mg	Propylene glycol, cc	Route	Interval prior to histamine	Death
1	3.75	F	100	1	i/v	20 min.	Within 15 min.
2	2.75	F	100	1	i/p	30 "	"
3	7.5	F	100	1	"	3 hr	"
4	5.5	M	100	1	"	5.5 "	"
5	5.9	F	2000	10	"	22 min.	"

TABLE II.
Effect of Multiple Injections of Rutin in Histamine Shock.

No.	Wt, lb	Sex	Rutin, mg	Amount and type propylene glycol medium	Route	Interval prior to histamine	Result
1	6.6	M	400	2.0 cc soln.	i/m	30 min.	Death within 15 min.
			"	" " "	i/v	" "	
			"	" " " "	"	15 "	
			"	" " " "	i/p	" "	
			1600				
2	3.75	F	100	5.0 " 10% emuls.	i/p	9 hr	"
			100	1.5 " soln.	"	8 "	
			150	2.25 " "	"	6 "	
			100	1.0 " 33% emuls.	"	5 "	
			200	5.0 " 10% "	"	3 "	
			200	1.0 " 50% "	i/m	" "	
			850				
3	5.25	F	100	1.0 " 33% "	i/p	9 "	"
			200	3.0 " soln.	"	8 "	
			40	0.4 " "	i/v	6.75 "	
			60	0.6 " "	i/m	" "	
			100	1.0 " 66% emuls.	"	5 "	
			200	1.0 " 50% "	"	3.25 "	
			200	" " " "	i/p	" "	
			900				
4	4.75	F	100	2.0 " soln.	i/v	25 "	"
			200	3.0 " 33% emuls.	i/p	23 "	
			100	1.0 " 66% "	i/m	22 "	
			100	" " " "	i/p	" "	
			200	" " 50% "	"	20 "	
			200	" " " "	i/m	" "	
			900				
5	5.5	F	100	1.0 " 33% "	i/p	72 "	"
			200	3.0 " soln.	"	71 "	
			100	1.5 " "	"	69 "	
			100	1.0 " 66% emuls.	i/m	68 "	
			200	" " 50% "	"	66 "	
			200	" " " "	i/p	" "	
			900				

At autopsy, Animals 2, 3, and 4 showed deposits of rutin at the injection sites.

to be 0.75 mg per lb. in 12 rabbits and this dosage level and the intravenous route used in all parenterally rutinized rabbits.

Previous studies in guinea pigs[8,9] have indicated that the anithistamine and anti-anaphylactic effects were confined to a brief

period some 10 to 30 minutes following administration of rutin. On this account, in the first group of rabbits, (Table I, No. 1, 2, 5; Table II, No. 1) the time interval between injections of rutin and histamine varied between 15 and 30 minutes. Under these circumstances no protection was observed, with up to 2000 mg of rutin. To exclude the possibility that the antihistamine effect of rutin in the rabbit is characterized by a long latent period (as is seen clinically in the treatment of abnormal capillary fragility states) an unstable emulsion of rutin was injected in addition to the solution and these were given repeatedly. The persistence of rutin deposits in 3 of 4 rabbits so treated, would appear to indicate that an extended absorption had taken place. Even with this procedure no antihistamine power could be found.

The complete results are presented in tabular form. In addition, 2 rabbits given 50 mg of rutin daily orally for 24 days, failed to survive a 0.5 mg per lb dose of intravenous histamine.

Summary and Conclusions. From the tables it can be seen that pretreatment with large doses of rutin, up to 2000 mg failed to protect rabbits against a minimum lethal dose of histamine. It therefore appears that in the normal rabbit, rutin is devoid of noteworthy antihistamine properties.

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Mouse Leukemia. XIII. A Maternal Influence that Lowers the Incidence of Spontaneous Cases.

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The discovery[1] of the milk factor as the cause of the difference in reciprocal hybrids between mouse strains of high and low incidence mammary cancer has naturally led to the search[2] for a similar agent to account for parallel differences between reciprocal hybrids between strains of high and low incidence of leukemia.[3] But evidence of a specific maternal factor inducing leukemia was not found. The question remains, what mechanism is responsible for the differences in reciprocal F_1 hybrids?

In the following experiment a high-leukemic strain C58, gens. 59-61, brother x sister, was crossed with a low-leukemic strain StoLi, gens. 54-57, brother x sister. (In a cross between such highly inbred strains, all first generation hybrids have the same genetic constitution.) The incidence of spontaneous leukemia was observed in 6 classes of F_1 females: namely, from reciprocal matings, fostered by nurses of strain C58, StoLi, or Balb. Each litter was divided among foster nurses of the 3 strains without receiving a drop of milk from its own mother. Each parturition was witnessed by one of a team of 4 observers† who maintained an uninterrupted, night and day vigil of each pregnant

* Diagnoses of cases doubtful in gross were contributed by Dr. M. N. Richter and Dr. R. A. Miller with technical assistance from Miss L. Lewis.

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