intraperitoneal hemorrhage. The jugular veins in both animals contained firm red thrombi. The 4 remaining animals were autopsied 48 hours after operation; both jugular veins were found to be occluded by firm thrombi in every case. In 2 additional rabbits blood-impregnated wool yarn was inserted into both jugular veins, but partial constriction of the vein by a metal clip was omitted. Determination of coagulation times and the administration of 10 mg of heparin intravenously twice daily as noted were also carried out in these animals. After 48 hours the jugular veins of both animals contained small thrombi with the colorless characteristics of "white thrombi."[1]

Dicoumarolized Animals. Seven rabbits were used in this series of experiments. Control prothrombin and coagulation times were established in each animal on 2 successive days. Following this a single excessive dose of dicoumarol† (100 mg) was administered by mouth. Prothrombin times were determined daily until the animal died or was killed. When the prothrombin concentration reached 20% or less of the control value (usually within 48 hours) insertion of a double strand of wool yarn as described above was carried out. In 3 of this group of animals a metal clip was placed on only one jugular vein; in the other 4 animals metal clips were placed bilaterally using the precautions to insure incomplete obstruction outlined above. Three of the animals died within 36-48 hours after operation from generalized hemorrhage. All the remaining animals were examined 48 hours after operation. All the jugular veins that had been constricted with a metal clip contained red thrombi indistinguishable from those in the untreated control animals. Of the 3 veins which had not been constricted by a clip, 2 contained thrombi distinctly smaller than those of the untreated controls; the third vein contained a thrombus the same size as in the controls.

Summary and Conclusions. 1. A method for the consistent production of experimental intravascular thrombosis is described. 2. The important role of stasis in the pathogenesis of thrombosis is emphasized. 3. The results show that the administration of heparin and dicoumarol in adequate doses to delay coagulation was not sufficient to prevent the development of experimental intravascular thrombosis in the presence of stasis of the venous circulation as induced in these experiments.

† Supplied by Abbott Laboratories through the courtesy of Dr. J. F. Biehn.

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Increased Resistance of Carrot-Fed Rats to Carbon Tetrachloride.

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The increased resistance of carrot-fed rats to acute anoxia has been reported by Campbell[1,2,3] and later confirmed by Nelson *et al.*[4] Since there is considerable evidence suggesting that the necrosis of the liver which follows the administration of carbon tetrachloride may be due to tissue anoxia, rather than to a direct toxic effect of the halogen hydrocarbon on the liver cells, it was decided to determine if a carrot diet would increase the resistance of rats to carbon tetrachloride. The possible protective action of charcoal was also studied as Campbell had shown that a high charcoal diet also increased the resistance of rats to acute anoxia.

Rats weighing from 150 to 250 g were used for all of the experimental work. In each individual experiment animals of the same sex

1 Campbell, J. A., *J. Physiol.*, 1938, **93**, 31.

2 Campbell, J. A., *J. Physiol.*, 1939, **95**, 1.

3 Campbell, J. A., *Quart. J. Exp. Physiol.*, 1939, **29**, 259.

4 Nelson, D., Goetzl, S., Robins, S., and Ivy, A. C., PROC. SOC. EXP. BIOL. AND MED., 1943, **52**, 1.

and of approximately the same size were used for both controls and experimental animals. The experimental animals were fed a diet of scraped raw carrots for a period of 7 to 10 days after which they and control animals on our stock diet were anesthetized with carbon tetrachloride in a previously described chamber.[5]

The animals were kept in the chamber about an hour and three-quarters when mortality studies were being done and about an hour and a half when the degree of protection was to be based upon the histological changes in the liver. In the latter cases, the animals were killed approximately 24 hours after anesthesia, the livers were removed and a portion of the large left lobe taken for histological examination after staining with eosin and hematoxylin. As a general rule in the experiments designed to study survival, no food was given for the first 24 hours following anesthesia. After this time Rockland rat diet was fed to both groups. The difference in the animal's desire to eat was always very marked. Most of the carrot-fed animals began to eat immediately after the food was put in their cage, while few control animals ever showed any desire to eat at that time.

The control animals in all experiments unless otherwise specified were white rats from our stock colony and were fed on Rockland rat diet. This diet has been used in our laboratory for a number of years and it has been our experience that an hour or so of anesthesia, or a maximum of an hour and three-quarters in the gassing chamber, would usually produce sufficient liver damage to cause the death of about 50% of the untreated animals. Early in the fall of 1944 a definite increase in the resistance of our stock animals was noted. This increased resistance was so great that only a slight difference could be noted histologically between the livers of the control and carrot-fed animals. The reason for this increased resistance is unknown but it is probably the same factor or factors present in carrots which increases the animal's resistance to carbon tetrachloride. A personal communication from the manufacturer states that the concentration of vitamins A and E in the diet was increased in the spring of 1944 but gives no other change. It is very doubtful if the increased content of vitamins A and E can explain the results which we have obtained. However, since we purchase our food every 2 or 3 months, it is probable that the increased resistance noted coincided with our purchase of the improved diet.

On account of this disconcerting situation it was decided to work with rats raised on a diet of known composition.* This diet has been used successfully for years by Dr. R. J. Main of the Department of Physiology in raising rats for vitamin D assay. It is low in vitamin D. The animals received about 10 g of greens per rat per week, in addition to the above diet up to the beginning of the experimental period. The results obtained with the animals raised on this diet were in complete agreement with those obtained previously using the unimproved Rockland rat diet. Survival data using the different diets are shown in Table I. No comparative survival experiments were carried out using the improved Rockland diet on account of the slight difference noted histologically.

In addition to these mortality studies over 50 rats raised on unimproved Rockland diets were used for comparative histological examination of their livers following exposure to carbon tetrachloride. The degree of liver damage was always less in the carrot-fed animals than in the corresponding controls, the results being in complete agreement with what one would expect from the mortality studies.

Attempts at fractionation of the carrots have led to inconclusive results. A carrot extract made with 95% alcohol when evaporated to a thick syrup at room temperature with the aid of a current of air and mixed with the Rockland diet usually imparted definite protective action to the diet. This protective action was lost if the extract was allowed to stand for several weeks at a tem-

[5] Forbes, J. C., and Neale, R. C., PROC. SOC. EXP. BIOL. AND MED., 1936, **34**, 319.

* Yellow corn meal 22%, wheat 19, wheat germ 4, soybean meal 19, dried skim milk 15, alfalfa 5, cotton seed oil 4, meat and bone meal 10, sodium chloride 1, calcium carbonate 0.5, and dried brewers yeast 0.5%.

TABLE I.
Effect of Carrot Feeding on the Resistance of Rats to Carbon Tetrachloride.

	No. of rats				
	Carrot fed		Controls		
Exp. No.	Lived	Died	Lived	Died	Control diet fed
1	4	0	0	4	Unimproved Rockland diet
2	3	0	2	1	" " "
3	4	0	2	2	" " "
4	6	0	1	5	" " "
5	6	0	3	3	" " "
6	4	0	2	2	" " "
7	4	0	1	3	" " "
8	8	1	2	2	" " "
9	5	0	0	5	Low vitamin D diet
10	6	0	0	6	" " " "
11	5	0	2	3	" " " "
	55	1	15	36	

perature not exceeding 10°C. Ground carrots dried on a steam bath also were inactive. The addition of either carotene, alpha tocopherol, thiamine, niacin, riboflavin, calcium pantothenate, a folic acid concentrate plus biotin, vitamin A and D as in Haliver oil (Abbott) or a combination of vitamins A, D, and E as in a 1 in 3 mixture of Haliver oil and wheat germ oil to the unimproved Rockland diet or to the low vitamin D diet did not demonstrably affect the protective quality of either diet.

In all the experiments where the possible effect of charcoal was being studied, the animals were given a diet consisting of 25% Norite-A and 75% unimproved Rockland diet. After the rats were 8-10 days on this diet, they, along with the controls, were anesthetized with carbon tetrachloride as previously described. The animals were killed approximately 24 hours after the time of anesthesia, their livers removed, sectioned and histologically examined after suitable staining. Although the charcoal-fed animals, on the whole, showed less liver damage than the corresponding controls the degree of protection was definitely less than that obtained with the carrot diet.

Summary. Rats fed a carrot diet for 7 to 10 days are definitely more resistant to the hepatotoxic effects of carbon tetrachloride than corresponding animals fed either a well-balanced stock diet, or a low vitamin D but otherwise well-balanced diet.

Admixture of activated charcoal at a 25% level with the stock diet endowed it with some protective action. The effect, however, was much less than given by the carrot diet.

We are indebted to Charles C. Haskell & Co., Inc., Richmond, Virginia, for a grant in aid of this research.