

Metabolic Studies in Patients with Gastrointestinal Cancer. III. The Hepatic Concentrations of Vitamin A.*

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In a previous communication¹ the fact was demonstrated that 85% of patients with cancer of the gastrointestinal tract had abnormally low plasma levels of vitamin A. In more than half of the patients this abnormality could not be explained by a deficient ingestion or malabsorption of the vitamin. Since there is considerable evidence to show that the liver is intimately concerned with the storage, distribution, and formation of vitamin A,² it was thought that the low plasma levels of the vitamin probably reflected, in those patients, hepatic insufficiency. Subsequently, it was demonstrated that a considerable degree of hepatic dysfunction did exist in patients with gastrointestinal cancer,³ but whether that dysfunction had resulted in a decreased capacity of the liver to store vitamin A or to distribute the vitamin properly, still remained unknown.

Recently an opportunity was presented to measure in patients with gastrointestinal cancer the vitamin A content of samples of liver removed at the time of laparotomy, and thus to ascertain whether or not the low levels of vitamin A in the plasma of the patients studied were due to decreased hepatic stores or to some other cause.

Clinical Material. The clinical material studied comprised 2 groups of individuals. The first consisted of 21 adults who were used as controls, 14 males and 7 females. Of the 21 individuals, death was due to skull fracture in 16, coronary occlusion in 3, gunshot in 1, and stab wound in 1. All these individuals were autopsied and sections of liver were obtained within 24 hours after death. Other than the immediate cause of death no gross pathological changes were noted.

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¹ Abels, J. C., Gorham, A. T., Pack, G. T., and Rhoads, C. P., *J. C. I.*, 1941, **20**, 749.

² Moore, T., *Biochem. J.*, 1931, **25**, 275.

³ Abels, J. C., Rekers, P. E., Binkley, G. E., Pack, G. T., and Rhoads, C. P., in press.

The second group was composed of 14 patients, 13 with gastric cancer and 1 with cancer of the colon. Ten were males and 4 females. Of the 14 patients, only 3 had been on grossly deficient diets before admission, and none had received preoperatively any vitamin A or other dietary supplement.

Methods. The method used for the measurement of plasma vitamin A is that described in the previous communication.¹

To measure the vitamin A content in the liver, samples of from 100 mg to 300 mg were obtained either at the time of laparotomy or at autopsy. All these samples were taken from the anterior margin of the right lobe. It is recognized that the distribution of the vitamin is not entirely uniform throughout the liver, but it was not feasible or permissible to obtain larger biopsy specimens for study.

As soon as each sample of liver tissue was obtained, it was placed in a tared weighing bottle in order to prevent loss of its weight by evaporation of water. After the weight of the tissue was calculated, the entire sample was homogenized in water and the resulting suspension diluted to 10 ml. Of this liver brei, from 1 to 4 ml were extracted with 10 ml of 95% alcohol and 10 ml of light petrol ether in a 50 ml centrifuge tube. Two ml portions of the petrol ether layer were removed for the determination of vitamin A by the same technic as that used for the determination in plasma. Hepatic concentrations of vitamin A are expressed in U.S.P. units per gram of wet weight.

The content of total lipids in the samples of liver brei was determined by the method of Van Slyke.⁴

Results. A. Concentration of Vitamin A in Livers of Individuals Used as Controls. It has been reported frequently that the vitamin A content per gram of normal human wet liver ranges from 200 to 1500 U.S.P. units.^{5, 6} Nevertheless, it was desirable to determine by the technic used in this investigation the range of vitamin A concentrations in the livers of the 21 individuals who were chosen as control subjects. The concentrations of the vitamin in their livers ranged from 186 to 1302 U.S.P. units and averaged 722 U.S.P. units per gram (Table I).

Whereas the vitamin A levels in the plasma of normal males is significantly higher than those of females, no such difference was

⁴ Van Slyke, D. D., Page, I. H., and Kirk, E., *J. Biol. Chem.*, 1933, **102**, 635.

⁵ Balli, E. P., Papper, E., Paley, K., and Bauman, E., *Arch. Int. Med.*, 1941, **68**, 102.

⁶ Bessey, O. A., and Wolbach, S. B., *The Vitamins*, Am. Med. Assn., Chicago, 1939, 30.

TABLE I.
Concentrations of Vitamin A in Livers of Individuals Used as Control Subjects.

Subject	Sex	Cause of death	Vitamin A U.S.P. units per g of liver	Microscopic examination of liver
F.S.	M	Coronary thrombosis	988	Normal
E.F.	M	" "	1302	"
E.R.	F	" "	1161	"
J.B.	M	Skull fracture	193	"
J.L.	M	" "	805	"
—	M	" "	1068	"
R.M.	M	" "	1202	"
M.Q.	M	" "	800	"
—	M	" "	186	"
A.F.	M	" "	234	"
—	M	" "	848	"
—	M	" "	989	"
—	M	" "	1006	"
—	M	" "	522	"
—	F	" "	577	"
—	F	" "	773	"
—	F	" "	939	"
—	F	" "	334	"
B.A.	F	" "	579	"
P.R.	F	Gunshot	445	"
—	M	Stab wound	227	No section
Average			722 U.S.P. units per g	

noted for the hepatic content of the vitamin. Of the 21 individuals, 14 were males and had hepatic vitamin A concentrations from 186 to 1302 U.S.P. units, and averaged 739 U.S.P. units per gram. The concentration of the vitamin in the livers of 7 females varied from 334 to 1161 U.S.P. units and the average was 700 U.S.P. units per gram. This range of values is in good agreement with those previously reported.

B. *Concentration of Vitamin A in Livers of Patients with Cancer of the Gastrointestinal Tract.* Since it has been found that 85% of patients with gastrointestinal cancer have plasma levels of vitamin A below the normal range, it was important to determine whether or not there also existed abnormal concentrations of the vitamin in the livers of those patients. Accordingly, 14 patients with cancer of the stomach and colon were studied (Table II). The hepatic concentrations of vitamin A ranged from 99 to 2236 U.S.P. units, and averaged 697 U.S.P. units per gram, or 97% of the normal value. Only 2 livers had concentrations below the control range.

On the other hand, of the 14 patients studied, the plasma levels of vitamin A were obtained in 10, and were found to be below the normal range in all but 1 instance. Eight of the 10 patients had distinctly low plasma levels of vitamin A associated with hepatic

TABLE II.
Concentration of Vitamin A in Liver and Plasma of Patients with Gastrointestinal Cancer.

Patient	Sex	Diet	Vitamin A, U.S.P. units		Liver total lipids, g per ml	Microscopic examination of liver
			Per g of liver	Per 100 ml plasma		
H.G.	M	Adequate	1347	95	6.6	Normal
G.P.	M	"	1072	105		Acute focal necrosis
L.G.	M	Deficient	786			Normal
D.S.	M	Adequate	1017	105		"
A.E.	M	"	2236			"
T.F.	M	"	713	120		"
J.Y.	M	"	196	135	3.3	"
L.S.	M	"	1226	75	7.3	"
J.R.	M	Deficient	99	40		"
E.W.	M	Adequate	242	85	6.2	"
F.R.	F	"	195	7	4.4	"
F.L.	F	"	337	90		"
K.P.	F	"	159	95	5.4	"
Y.B.	F	Deficient	948			"
Average			697	U.S.P. units per g		

concentrations of the vitamin which were within the control group.

It has been found here and elsewhere⁵ that the fatty livers of patients with chronic alcoholism contain considerably less vitamin A than do those of normal individuals. It would appear, therefore, that the low plasma level of the vitamin in patients with fatty livers is not due to the fact that the fat-soluble vitamin A was withheld from the blood. Nevertheless, it was of interest to determine whether or not the livers of patients with gastrointestinal cancer had an abnormally high content of lipids. The liver total lipids, accordingly, were determined in 6 of the 14 patients studied, and were found to range from 3.3 to 7.3 g %—well within the normal limits.⁷ This finding thus would eliminate the possibility that the low levels of vitamin A in the plasma of patients with gastrointestinal cancer were due to an abnormally high content of liver fat with consequent hepatic retention of the fat-soluble vitamin A.

Discussion. This study was undertaken to determine whether or not the low levels of vitamin A in the plasma of patients with gastrointestinal cancer were due to an inability of the livers of those patients to store the vitamin. The results presented here indicated that there is no gross defect in the hepatic storage of the vitamin in these patients to explain the corresponding low plasma levels. Therefore, another explanation must be sought, and the possibility has been considered in the previous communication¹ that the livers of

⁷ Ralli, E. P., Rubin, S. H., and Ringler, S., *J. C. I.*, 1941, **20**, 93.

patients with gastrointestinal cancer might not be able to distribute the vitamin normally. It was demonstrated that the administration of choline, yeast, or lipocaic could raise the levels of the vitamin in the plasma. Since both yeast and lipocaic are known to contain choline, their activity conceivably might be due to that compound, and it is possible that in these patients there might exist a deficiency of a substance with a choline-like activity. This possibility still has to be investigated.

Conclusions. The low plasma levels of vitamin A of patients with cancer of the gastrointestinal tract probably are not due to a decreased capacity of the livers of those patients to store the vitamin.

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Relation of Arterial Pulse-Pressure to Arterio-Venous Oxygen Difference, Especially in Arterial Hypertension.

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Pulse-pressure in the brachial artery is no longer regarded as a rough measure of cardiac output. Nor can we assume that it gives information concerning what is happening in other arteries. Further, arterial distensibility decreases and pulse-pressure increases as internal pressure is raised, although deviations due to this factor are small in the range of human blood pressures.¹ Comparisons involving pulse pressures from different individuals (varying in size of vessels, muscle masses, metabolic rates, etc.) taken under varying conditions of temperature, humidity, etc., would seem, therefore, to have little justification.

In spite of these considerations an attempt was made to correlate certain data in our possession obtained from 47 patients suffering from a variety of diseases. In Fig. 1 the arterio-venous oxygen differences have been plotted against the products of the pulse pressure multiplied by pulse rate ($PP \times PR$) as ascertained on the brachial artery. Venous blood was drawn from the median basilic vein. It will be seen that most of these cases fall within a curved area (AA), the mean of which is roughly represented by a curve (DD) such that, for any point on the curve,

¹ Hallock, P., and Benson, I. C., *J. Clin. Invest.*, 1937, **16**, 595.