thromboplastin argues that the action of thromboplastin is a specific one. The thromboplastin, although relatively crude, was prepared for its cephalin content. Thus, the effect of thromboplastin is due either to the action of cephalin or to some other substance present in the rather crude extract. Since the two phospholipids are closely allied structurally, the possibility of a caloric influence is eliminated, for these substances are virtually isodynamic and any other material contained in the crude extract which might have this effect would be so low in its concentration as to be negligible from this standpoint.

Data on the mechanism of action must await purification of the active principle. However, the experiments of Glenn, Peterson, and Drinker[10] recently reviewed by Cope[11] prove that thromboplastin is absent in burn edema fluid. In the light of our results this fact would indicate that the function of the injected thromboplastin is to augment the supply of this substance and thus to prevent excessive transudation and fluid loss. An experiment performed to determine whether the material was effective if administered after shock had ensued yielded equivocal conclusions. The animals treated with thromboplastin seemed to die faster than saline-treated animals, indicating that the material was toxic to shocked mice. The crude saline extract of cattle brain contains substances which are inactive as far as *normal* mice are concerned, but such compounds as histamine, which are present in these preparations, will become markedly harmful if they are administered at a time when the animal's normal detoxifying systems have been deranged by burn shock. Further purification is necessary to establish whether the toxicity of the crude preparation is responsible for its lack of efficacy when administered after shock has once been established, or whether some physiological intermediate present in normal animals but damaged in shocked mice, is blocked so that administration of a precursor is ineffective.

Conclusions. 1. Mice injected intraperitoneally with a 1% suspension of thromboplastin in isotonic saline solution showed a greater mean survival period than mice injected with either isotonic saline or with a 1% suspension of lecithin in isotonic saline. 2. Mice receiving thromboplastin showed a higher ultimate survival rate than those receiving either lecithin or saline. 3. Analysis by chi^2 showed a significant difference between thromboplastin and saline but not between lecithin and saline. 4. Intraperitoneal injection of thromboplastin one hour after traumatization of the animals seemed to exert a toxic effect.

The authors wish to express their appreciation to Mr. Frank Lanni for the figure.

10 Glenn, W. W. L., Peterson, D. K., and Drinker, C. K., *Surg.*, 1942, **12**, 685.

11 Cope, O., *J. Am. Med. Assn.*, 1944, **125**, 536.

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Nutritional Macrocytic Anemia: Response to a Substance Other Than the Anti-Pernicious Anemia Principle.*

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Recent publications[1-7] indicate a difference

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1 Napier, L. E., Das Gupta, C. R., Chaudhuri, R. N., Sen, G. N., Rai Chaudhuri, M. N., Sen Gupta, P. C., and Majumder, D. N., *Indian Med. Gaz.*, 1938, **73**, 385.

2 Wills, L., and Evans, B. D. F., *Lancet*, 1938, **2**, 416.

3 Davidson, L. S. P., Davis, L. J., and Innes, J., *Brit. Med. J.*, 1942, **2**, 31.

TABLE I.
Positive Hematopoietic Effect of Orally Administered Liver Extract Following Negative Effect of Parenterally Administered Liver Extract.

Days of treatment	Case 1 R.B.C. (mils)	Case 1 Retics. (%)	Case 2 R.B.C. (mils)	Case 2 Retics. (%)	Case 3 R.B.C. (mils)	Case 3 Retics. (%)
	Liver Inj.—Lederle 10 U.S.P. units i.m. alternate days		Reticulogen—Lilly 1 cc and Liver Inj. (Crude)—Wilson 4 U.S.P. units i.m. daily		Special Liver Preparation* 5 cc i.m. daily	
0	1.42	0.4	3.07 (T)†	0.4	1.72 (D) (T)	0.6
2	1.03 (T)	0.4	2.56	1.0	1.57	0.0
4	1.36	0.2	2.65	0.4	1.78	0.0
6	1.21 (T)	0.2	—	0.5	1.52	0.2
8	3.50 (T)	0.2	—	0.9	1.28	0.2
	Liver Inj. (Crude)—Wilson 5 U.S.P. units i.m. daily				Same Preparation 51 cc 1 U.S.P. unit orally daily	
10	3.00	0.0	2.92	1.6	1.27	2.6
			Liquid Ext. Liver—Valentine‡ 1 U.S.P. unit orally daily			
12	3.26	0.2	—	1.6	1.26	8.4
14	3.37	0.0	3.02	3.2	1.46	26.2
16	3.15	0.1	3.45	13.0	1.67	16.0
18	3.50 (T)	0.0	3.65	6.2	1.97	16.6
	Liquid Ext. Liver—Valentine‡ 1 U.S.P. unit orally daily					
20	3.19	0.1	3.22	2.2	2.25	12.2
22	3.50	0.4			2.72	12.6
24	3.08	1.7			2.48	7.5
26	3.27	2.6			2.97	7.3
28	3.26 (T)	4.5	3.90	—		
30	3.46	6.5				
32	3.45	3.8	4.10	—		
34	3.54	4.5			3.38	3.8
36	4.10	3.8				
47 (D)	4.03	2.5				

* Liver Extract—Lilly, of which 12.75 g constitute 1 U.S.P. unit (oral), was kindly supplied by Mr. George B. Walden of Eli Lilly and Company. This material was suspended in water at pH 6.8 and sterilized by boiling. Each cc of the suspension solution contained 0.25 g of the original preparation.

† (T) = transfusion; (D) = delivery.

‡ Kindly supplied by Mr. Braxton Valentine of Valentine's Meat-Juice Company.

between the basic nutritional deficiency in Addisonian pernicious anemia and in certain macrocytic anemias usually associated with pregnancy and encountered in both the tropics and the temperate zone. Thus, in the latter no response was observed following parenterally administered liver extracts of known effectiveness in pernicious anemia but rapid blood regeneration was said to occur when liver extract, liver, or autolyzed yeast was given by mouth. Because paucity of hematological controls renders some of these interesting reports difficult of interpretation, observations were made on 3 female patients with nutritional macrocytic anemia apparently of this unusual type.

Cases 1 and 3 became anemic during pregnancy. All gave histories of striking dietary inadequacy, showed free hydrochloric acid in

[4] Miller, H. G., and Studdert, T. C., *Lancet*, 1942, **2**, 332.

[5] Fullerton, H. W., *Brit. Med. J.*, 1943, **1**, 158.

[6] Davidson, L. S. P., Davis, L. J., and Innes, J., *Edinburgh Med. J.*, 1943, **50**, 431.

[7] Nielsen, O. P., *Acta med. Scandinav.*, 1941, **108**, 421.

the gastric contents, and had macrocytic and slightly hypochromic anemia with moderate leukopenia and thrombocytopenia. Anisocytosis and poikilocytosis of red blood cells were less marked than in equally anemic cases of pernicious anemia. The differential white counts were normal. There were no neural manifestations. The methods of dietary control and of blood counting[8] and the interpretation of daily counts of reticulocytes[9] made during successive test periods have been described elsewhere.

The hematological data summarized in Table I appear to demonstrate that prompt response to orally administered liver extracts immediately followed therapeutic failure of liver extracts given parenterally, even in multiple U.S.P. units[10] daily. Cases 1 and 2 responded to liver extract given orally after failing to respond to more refined preparations of known effectiveness in pernicious anemia given intramuscularly. This demonstrates in these patients a deficiency of some substance other than the principle effective in pernicious anemia. Case 3, unlike patients with pernicious anemia, responded to a special preparation of Liver Extract—Lilly only when it was given orally in 10 times the amount that was ineffective on intramuscular injection. This suggests that the tenfold increase in oral dosage was the cause of the therapeutic success, and eliminates as an explanation of therapeutic failure following parenteral administration a difference in chemical properties of the preparation used. The fact, however, that in pernicious anemia an aqueous solution of Liver Extract—Lilly has been found to be 60 times as active hematopoietically when injected as when given by mouth,[11] suggests an alternative explanation: Possibly the digestive organs in this type of patient form a new hematopoietic substance from the liver extract in a fashion analogous to the food-gastric factor relationship in Addisonian pernicious anemia.[8,12]

As was first pointed out for tropical macrocytic anemias,[1,2] in such exceptional patients as are here reported the basic nutritional deficiency differs from that in patients with Addisonian pernicious anemia. Consequently, the "unitarian" hypothesis concerning the etiology of pernicious and other nutritional macrocytic anemias, suggested by Strauss and Castle,[12] does not apply to these particular patients. This distinction emphasizes the desirability of a therapeutic trial of *orally administered* liver extract in macrocytic anemias, particularly those of pregnancy, when they are refractory to parenterally administered liver extracts.

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8 Castle, W. B., and Ham, T. H., *J. A. M. A.*, 1936, **107**, 1456.

9 Minot, G. R., and Castle, W. B., *Lancet*, 1935, **2**, 319.

10 U.S.P. Anti-Anemia Preparations Advisory Board: Third Announcement, *J. Am. Pharm. Assn.*, Practical Pharmacy Edition, 1940, **1**, 53.

11 Strauss, M. B., Taylor, F. H. L., and Castle, W. B., *J. A. M. A.*, 1931, **97**, 313.

12 Strauss, M. B., and Castle, W. B., *New Eng. J. Med.*, 1932, **207**, 55.