acid and *p*-aminobenzoyl-*l* (+)-glutamic acid, the names pteroic acid and pteroylglutamic acid are suggested.

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Famine Edema and the Mechanism of Its Formation[1]

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Edema associated with severe undernutrition was widespread in Europe during and shortly after World War I. No adequate explanation from infectious, cardiac, or renal causes was found. Speculation as to the mechanism of formation of this edema subsided with the demonstration that edema can be provoked in animals by a very low protein diet and with the accumulation of evidence for the general validity of Starling's concept of a filtration balance between hydrostatic and colloid osmotic pressures at the capillary wall. Despite some puzzling facts (*10–12*), by the eve of World War II there was almost universal agreement that "famine edema," as in kidney disease, is produced by a profound depression of the plasma colloid osmotic pressure, this in turn being a result of inadequate dietary protein.

In World War II, as expected, famine edema again appeared on a large scale. Contrary to expectation, however, the theory of simple hypoproteinemic causation was not fully sustained in such observations as were made (*4, 7*), though there was reluctance to abandon entirely this attractive theory (*1, 5, 6, 9*). Data gathered by the Allied Armies indicated that hypoproteinemia was common in famine areas but that it was generally slight in degree and was not closely related to the appearance or severity of edema (*3, 13*).

In this laboratory data were obtained from a controlled experiment with 34 men (volunteers from civilian public service), who subsisted on a European type of famine diet for six months preceded by a control period of three months and followed by three months of controlled "relief" feeding. The diet of whole cereals, potatoes, turnips, etc. provided an average of 49 grams of protein daily and proved to be closely similar to the diets in the less fortunate parts of western Europe in early 1945. These men lost an average of 24.5 per cent of their body weight. Pitting edema appeared within two months in some of the men and eventually in all but a few of the group; even the few apparent exceptions were shown, by special means, to be "waterlogged." At the end of semistarvation the thiocyanate method indicated an average SCN^- space of 34.0 per cent of the total body weight and a relative excess of 7.19 kg. (15.9 lbs.) of extracellular water per man. In proportion to the non-SCN^- space, the extracellular water rose from a "normal" average of 282 grams/kg. of cellular tissue to a "starvation" average of 554 grams/kg.

This development of edema was accompanied by only a small decline in plasma protein concentration, averaging 0.73 grams/100 cc. At the same time the ratio of albumin to globulin decreased to only a trivial extent. Independent analyses by the Tiselius electrophoresis method (veronal buffer) gave an average A/G of 2.00 for the heparinized plasmas of six men who showed marked edema. The same method, when applied to serum, gave A/G values of 1.70 and 1.89 for two of these men. Heparin has a slight influence on the Tiselius pattern which will be reported subsequently.

Clinical edema vanished during three months of refeeding which produced an average recovery of 37 per cent of the lost weight. At the same time the plasma protein concentration returned to normal, but there was a slight fall in A/G; by the Tiselius method A/G averaged 1.82 in the heparinized plasmas of the six men mentioned above. Clearly, the edema was not explicable in terms of hypoproteinemia or subnormal colloid osmotic pressure in the plasma, even with "correction" for protein in the interstitial fluid; edema fluid in this condition is extremely low in protein.

These subjects, like the victims abroad, showed a marked polyuria, profound bradycardia, and no rise in the concentrations of nonprotein nitrogen and chloride in the plasma. The liver was not palpable, and the heart was much diminished in size by X-ray examination. Thiamine deficiency was definitely ruled out by the analysis of food and excreta for thiamine, the reduced size of the heart, and by the absence of signs of polyneuritis. Direct measurements of venous pressure showed that, instead of an increase, there was a markedly subnormal level. At the end of semi-

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starvation the mean supine venous pressure in 32 men was 4.80 cm. of saline solution with the needle in an arm vein and the manometer zero at 10 cm. above the table level. Control measurements on 12 normal men gave averages of 9.7 and 10.3 cm. on two occasions five months apart. Data on two of the subjects who showed only moderate clinical edema after six months of semistarvation are given in Table 1. During refeeding, the venous pressure gradually rose to normal values.

TABLE 1

	Body wt. (kg.)			SCN- Space		Plasma Prot.		Ven. Press. Cm.
Subject No.	Control	Starv.	Diff.	% Wt.	Edema* Kg.	Grams/100 cc.	A/G	Saline
109	79.3	59.5	−19.8	31.0	5.4	6.44	1.79	4.8
112	61.4	49.0	−12.4	32.3	5.0	6.78	2.01	4.5

* The figure for "edema" represents the excess extracellular water as calculated from the proportion in the normal state.

The more prominent factors in the Starling concept of edema formation would not seem to explain famine edema unless we accept the unlikely hypothesis of a remarkable hydrostatic pressure gradient between the capillary and the larger veins. Parenthetically, it may be noted that there was a moderate arterial hypotension at both systole and diastole. Of the items in the Starling equation as elaborated by Schade and Claussen, Krogh, and others, there remains only the tissue pressure. Youmans, *et al.* (*12*) emphasized this neglected factor in their attempt to explain endemic edema in Tennessee, but their calculations as to the magnitude of this pressure have been properly rejected (*2, 8*). Although we must agree that there is great uncertainty about the actual tissue pressure at the site of filtration, normally it is probably only a small fraction of the plasma colloid osmotic pressure. From digital examination it appears that the tissue pressure in starvation is subnormal, but even a profound decline could scarcely surpass 10 per cent of the intracapillary pressure. By exclusion, then, it appears that the balance between blood plasma and interstitial fluid does not represent a simple equilibrium, as is customarily postulated.

The assumption of actual equilibrium in such a dynamic situation as that at the capillary wall would seem to be unduly optimistic on *a priori* grounds. The fact of lymph flow is itself an indication of imperfect balance. It is well known that the prediction of rates of reactions or other events in nonequilibrium states from equilibrium equations is both hazardous and complicated. There is no reason to believe that the exchange between plasma and tissue fluid is an exception.

Summary

Famine edema was produced experimentally in 34 normal men who lost a quarter of their body weight while subsisting for 6 months on a European type of semi-starvation diet. The ratio of extracellular water to cellular tissue was roughly doubled. Their clinical state closely resembled that seen in Europe in 1945. There were no signs of renal or cardiac failure. The plasma protein concentration fell only slightly and the A/G ratio remained within normal limits. The venous pressure was roughly 50 per cent below normal. Data from the field lend support to these indications that famine edema is not simply a result of hypoproteinemia or of renal or cardiac failure. It is concluded that there is a dynamic nonequilibrium state of the capillary wall and, accordingly, calculations from equilibrium equations are inadmissible.

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Antibacterial Action of Phenanthrene-related Substances

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Intrapleural injection in tuberculous empyema (some mixed infected) of a vitamin A and D concentrate, considering it as a topical application of the cod-liver oil vitamins, resulted in disappearance of the pathogenic organisms (*4*).

In further clinical work, vitamin D alone proved to be responsible for the antibacterial action against tubercle bacilli, *Proteus vulgaris, Bacillus aerogenes,* nonhemolytic streptococcus, and *Staphylococcus aureus.*

In vitro vitamin D inhibited the growth of tubercle bacilli if added (50 units/cc.) to the culture media (Hohns, Loewenstein, Corpers Potato Media). By using the plating method, *Staph. aureus, P. vulgaris,*