resistance during treatment and clinical improvement, the asymptotic concentration for complete lysis unquestionably tends to fall towards the normal figure, but much more slowly than the clinical improvement takes place.

A number of typical results are shown in Table I.

These changes in resistance are observed not only with saponin (British Drug Houses), but when sodium taurocholate at pH 7.0 or sodium glycholate at pH 6.0 are used as lysins. The results clearly indicate that the red cells from the blood of cases of pernicious anemia are more vulnerable to the action of such lysins *in vitro* and probably *in vivo* also, and we are calling attention to them so that those who have access to clinical material may extend the observations.

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Cod Liver Oil Therapy in Experimental Tuberculosis.*

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Cod liver oil has been used from time immemorial by fisherfolk for the treatment of external wounds, and it has long been recommended for the treatment of tuberculosis. Löhr,[1] studying the wound healing properties of cod liver oil in various types of wounds, reported that this oil would aid in the healing of lupus. Our interest in the influence of cod liver oil on tuberculous lesions was especially aroused by the report of its successful use in the treatment of 3 cases of lupus by Banyai.[2]

Our purpose was (1) to confirm, if possible, the clinical observations on man by studying the effect of cod liver oil on tuberculous skin ulcers in guinea pigs, and if the results should prove favorable, (2) to isolate the chemical fraction in the oil responsible for the healing action, (3) to study its effect on other types of experimental tuberculosis, and (4) if these experiments should be satisfactory, then to determine the effect of the "pure substance" in human tuberculosis.

Tuberculous skin ulcers were produced by the intracutaneous in-

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1 Löhr, Wm., *Wundheilung*, 1937.

2 Banyai, Andrew L., personal communication, 1935.

jection of 0.2 mg of virulent tubercle bacilli (H37) and treated topically twice daily with a few drops of cod liver oil. Our first experiment, using 24 animals, verified the clinical observations in that the lesions in the treated animals healed more rapidly than those in the controls. Each animal received 3 cc of the bacterial suspension standardized by the method of Breed and Breed as given by Baldwin.[3] At 2 weeks induration was noted; ulcers approximately 1 cm in diameter were present at 3-4 weeks. Treatment was started on the 28th day of infection and lasted until the lesions were closed or until the experiment was terminated 30-40 days later. If pus was present, it was wiped out with a sterile swab both in the control animals and in the treated animals before application of the oil. This experiment has been repeated 6 times using a total of 86 cod liver oil treated animals; the ulcers have always healed faster than those of the 89 controls. (See Fig. 1.) Various other oils; namely, paraffine, lanum, olive, and cottonseed (Wesson) have been tested and all proved ineffective. Cod liver oil has been administered orally, intramuscularly, and subcutaneously, and all routes except the oral have been found effective.

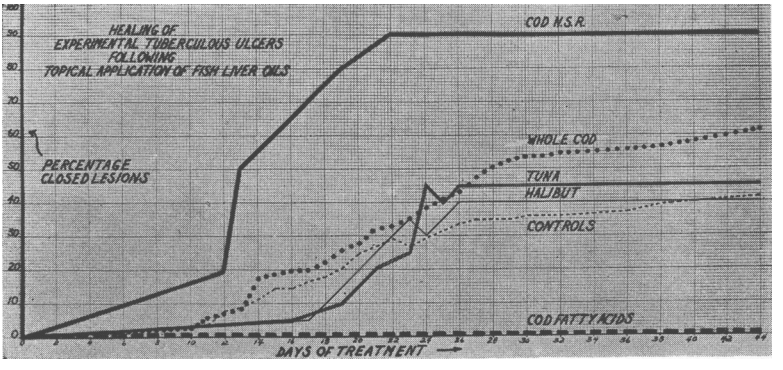

FIG. 1.

Chemical fractionation of the oil was then begun by saponification. The fatty acid fraction was found to be non-healing, in fact, quite irritating. Rancid oils produce the same reaction and so does lanum when treatment of the tuberculous ulcers is prolonged. The active agent is concentrated in the non-saponifiable residue (NSR) *since it causes healing faster than the whole oil,* often as early as the 12th day of treatment (See Fig. 1) and with remarkably little scar tissue. Early in the work it was learned that cod liver oil pro-

[3] Baldwin, E. R., Petroff, S. A., and Gardner, L. S., *Tuberculosis*, 1927, p. 60.

duces a systemic effect rather than merely a local response, as the treated animals show less generalized tuberculosis than do the controls. The NSR administered topically or intramuscularly exerts a similar but more marked effect.

Next, the NSR was fractionated by rapidly precipitating the heavy sterols from a methyl alcohol solution with carbon dioxide snow. The precipitate of the heavy sterols was inert; and the filtrate designated the "vitamin fraction" proved to be active. This so-called "vitamin fraction" has two known constituents, vitamins A and D, and numerous unknown substances.

The investigation was continued, therefore, by testing 3 different oils† varying greatly in vitamin A and D content; halibut liver oil with 50,000 A units and 200 D units; tuna liver oil with 70,000 A units and 88,000 D units; and a control cod liver oil with 1,800 A units and 175 D units per gram. Assuming the oils to be comparable in other respects, if vitamin A were the factor, halibut and tuna liver oil should be more effective than the cod; if vitamin D were the desired agent, then tuna liver oil should induce more rapid healing. *Cod liver oil proved to be the superior healing agent* (Fig. 1), and further, the other 2 oils showed no favorable systemic effects.

Especially interesting is a recent publication by Dykes[4] reporting that cod liver oil is definitely superior to halibut liver oil in the treatment of wounds of different types.

The results here reported, using 1400 guinea pigs in 8 series of experiments, indicate that in the "vitamin fraction" of cod liver oil resides an agent which exerts a favorable healing action in tuberculous ulcers. Chemical and biological study of this fraction is being continued.

† All of these oils were supplied through the courtesy of Dr. Warren M. Cox, Jr., of Mead Johnson and Company.

[4] Dykes, George, *Vet. Rec.*, 1937, **49**, 649.