several interesting relationships exist, especially those concerned with inhibition of the enzyme. It has been suggested by Lerner and Fitzpatrick(4) that sulfhydryl groups of glutathione and cysteine inhibit tyrosinase by binding the copper. It has also been postulated that in addition to the sulfhydryl compounds, the high oxidation potential of other substances also influences the copper containing enzymes so that they are unable to function optimally.

This paper does not provide data nor is any information available on the effect of folic acid antagonists on tyrosinase or on tyrosine metabolism, but several authors have pointed out the relationship of both folic acid and ascorbic acid to increased excretion of "tyrosyl" compounds. Woodruff and Darby (5) have shown that the increased excretion of "tyrosyl" compounds in scorbutic guinea pigs could be corrected either with ascorbic acid or folic acid. Evidence already exists that folic acid is concerned with tyrosine metabolism since Govan and Gordon(6) showed earlier that the premature infant's inability to cope with a high protein diet resulted in increased excretion of "tyrosyl" compounds which could be corrected by folic acid therapy or by ascorbic acid administration(7) and Johnson and Dana(8) have shown that ascorbic acid given to folic acid deficient rats can modify the loss of weight after the deficiency is induced by a diet containing sulfasuxidine. The chemical relationship of tyrosine to adrenochrome compounds also permits speculation regarding the role of the adrenal glands in the pigmentation of our patient. Since tests for adrenocortical function were all within normal limits, the possibility of an Addisonian type of pigmentation is unlikely in our patient.

Summary. Hyperpigmentation of the skin has been observed in several cases of acute leukemia receiving folic acid antagonists and histological studies in one patient confirmed the impression that true melanogenesis had occurred. The role of antagonists in influencing the tyrosinases concerned in melanin formation is unknown.

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Role of Detergent Complexes in Experimental Gastric and Duodenal Ulcers.* (18190)

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Dogs injected with histamine by the method of Code and Wangensteen(1) develop a gastric hypersecretion, "peptic" ulcers, and usually expire within two weeks. Shoch(2) produced ulcers in 70% of all animals when he subjected them to daily intramuscular injections of 30 mg of histamine base in beeswax and mineral oil. The average survival time was 17 days. He later produced perforated ulcers in 100% of the animals within 9 days using the same regime. Shoch pre-

* This research was partly supported by a grant from E. I. du Pont de Nemours & Co. who also prepared the RD-11 detergent complex.

1. Varco, R. L., Code, C. F., Walpole, S. H., and Wangensteen, O. H., *Am. J. Physiol.*, 1941, v133, 475.

2. Shoch, D. E., Ph.D. Dissertation Northwestern University, 1943.

vented or reduced the occurrence of these conditions in dogs by administering 0.1 g sodium alkyl sulfate hourly.

The present investigation was undertaken to produce inactivation of enzymes by detergent complexes and to study the changes in composition of gastric secretion produced by oral administration of detergent complexes. The detergent complex used as the medicant in this experiment was sodium alkyl sulfate bound to gastric mucin (Mucosulf). Dogs medicated with 900 mg of Mucosulf only twice daily showed similar changes (*i.e.* reduced incidence of ulcer, increased survival time, and altered gastric juice formation) to those produced by Shoch using nearly twice the quantity of medicant given at hour intervals.

Experimental. The investigation was begun on November 14, 1949 and terminated 216 days later. Sixteen dogs were injected with 30 mg of histamine base intramuscularly. Of the total number of dogs, 10 were injected as described for 3 days only and their gastric secretions were used as an additional control to that obtained from the other 6 dogs for the same length of time. Beginning on the fourth day 6 dogs were given orally two 900 mg doses of Mucosulf daily after each injection of histamine while the other 10 dogs were dropped from the experiment.

There was a slight transient illness in most dogs around the fourth day. Symptoms of diarrhea, melena, and anorexia lasted for about 3 days after which the dogs became apparently normal as they remained through the entire period of medication. It is possible that an ulcer may have formed but that it soon healed.

Gastric secretions were collected through an Ewald tube on the second and third day on histamine. These served as the control. After beginning medication gastric samples were taken once every 2 weeks for the duration of the experiment. On the day of collection the first gastric sample was withdrawn 3 hours after the administration of the histamine and Mucosulf. This sample was designated the residuum. The second sample was taken one half hour after the first. The stomach was emptied in each case and the volumes recorded as total volume.

Aliquots were taken from the total volume for analysis of the total available acid (in mg HCl), pepsin (in pepsin units), mucin (in mg glucose) and lysozyme. Aliquots were also taken to determine the concentration of pepsin (in units per ml of gastric juice), mucin (in mg per ml of gastric juice), lysozyme (in μg per ml gastric juice), the pH, and viscosity (relative to distilled water). The mucin was determined according to the method of Anderson, Fogelson, and Farmer (3), the lysozyme by a modified Smolelis and Hartsell(4) method, and the pepsin by the method of Anson and Mirsky(6-8).

Mucosulf medication was stopped after 165 days and within a period of one month all but 2 of the dogs expired. Autopsies showed deep erosions, hemorrhagic gastritis, and perforating ulcers indicated that death was due to peritonitis.

Discussion. Lysozyme, mucin and viscosity assays were made following Meyer's observation(5) on lysozyme and its relationship to gastroduodenal diseases. It was found that during the Mucosulf medication there was a marked reduction in the total available lysozyme in the gastric juice without any significant change in its concentration and that the concentration of mucin and the degree of viscosity increased. When medication was stopped a rapid increase in total available lysozyme occurred with no change in its concentration. Also the mucin concentration and degree of visosity were low.

In Fig. 1, 2, 4, and 5 the gastric juice components from dogs on Mucosulf therapy fall below the variation of the control therefore there is a definite decrease in the re-

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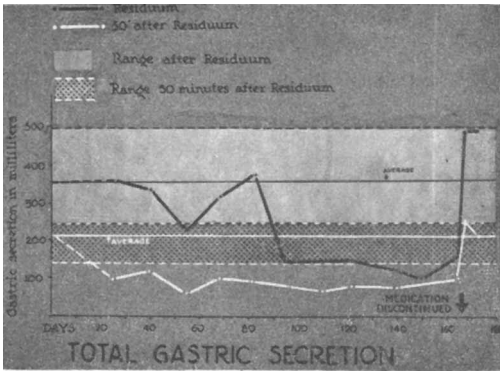

FIG. 1.

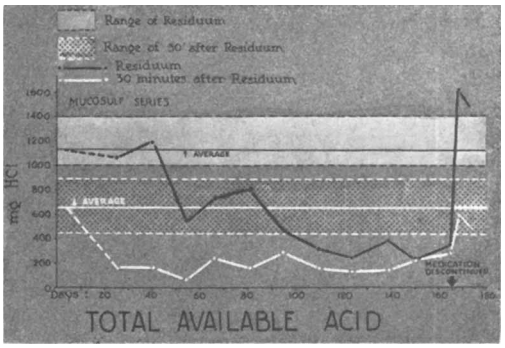

FIG. 2.

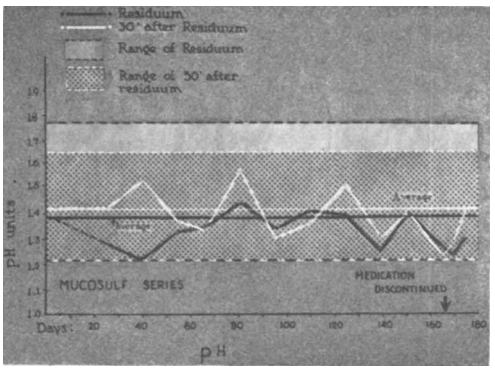

FIG. 3.

spective components of the gastric juice as a result of mucosulf therapy. However, in Fig. 3 all pH values fall within the normal variation. There was therefore, no significant change in pH as the experiment proceeded.

Each point on the figures represents the average of 6 dogs. The use of this average is considered permissible since it was shown statistically that individual variations between the dogs were not greater than the daily variations of a single dog. The solid horizontal lines on each figure represent the average of the controls while the area between the dotted lines is the range of variation.

From these data it is evident that there is a decrease in total pepsin as well as in pepsin concentration but only a decrease in total available gastric acidity not in its concentration. Therefore it appears that pepsin rather than acidity plays the primary role in experimental ulcer formation. Hence medication may well be directed toward reduction of enzymatic activity.

A second investigation is in progress using the detergent complex, sodium alkyl sulfate bound to a resin (RD-11), as the medicant.

Summary. The results obtained from mucosulf therapy of experimental ulcer for-

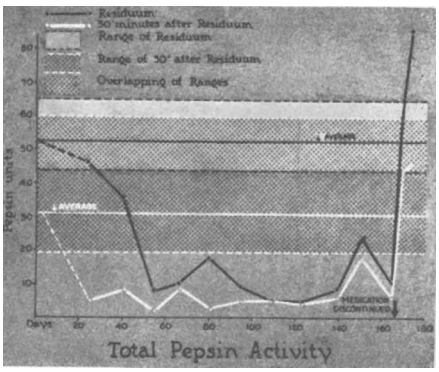

FIG. 4.

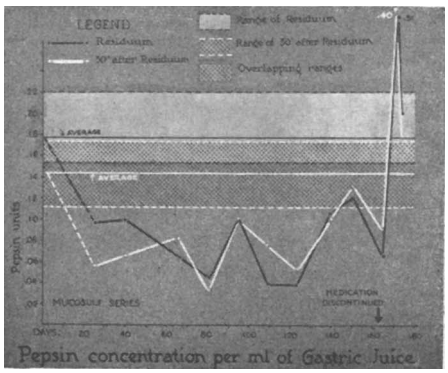

FIG. 5.

mation show that there is a decrease in total available pepsin and in pepsin concentration, but only a decrease in total available gastric acidity and not in its concentration. Total available lysozyme was decreased but not its concentration. The volume of gastric juice was decreased while its viscosity was increased. Total available mucin was increased as was its concentration.

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Effects of Cortisone, Hyaluronidase, Desoxycorticosterone, and Artisone on Experimental Serum Disease in Rabbits. (18191)

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In previous experiments it was shown that large doses of colchicine or nitrogen mustard depress or prevent the Arthus reaction in the skin and the allergic arteritis and valvulitis caused by horse serum in rabbits(1,2). As this was associated with depression of precipitin formation, and enlargement of the adrenals and shrinkage of the thymus (alarm reaction), it was postulated that the beneficial effect of the drugs in this disease was due to destruction of antibody forming cells through the mediation of the adrenal cortices(1). Recently it was demonstrated that 10 to 20 mg of adrenocorticotrophic hormone (ACTH) per day likewise depressed the Arthus reaction, allergic arteritis and endocarditis, the weight of the thymus, and precipitin formation(3). There is reason to believe that these effects are produced by the glucocorticoids, which also influence permeability of the ground substance(4), the site extensively involved in serum disease. We considered it desirable, therefore, to compare the effect in serum disease of cortisone, which causes both lymphoid involution and changes in permeability of the ground substance, with hyaluronidase, desoxycorticosterone acetate (DCA), and 21-acetoxypregnenolone (Artisone), which also alter ground substance permeability but do not affect lymphoid tissue.

Materials and methods. All experiments were performed in young male albino rabbits weighing between 1760 and 2500 g. One series of 40 rabbits was given by intravenous injection 15 ml of normal horse serum without preservative per kg of body weight. Three groups of 10 animals each received 4 mg cortisone acetate,* 2.5 mg DCA,† and 5 mg Artisone acetate‡ twice daily by intramuscular injection; the remaining 10 animals served as serum controls. Another series of 20 rabbits received 10 ml horse serum per kg. Ten of these received 6000 turbidity reducing units (T.R.U.) of hyaluronidase§ per kg of body weight (twice daily by intravenous injection); the other 10 served as serum controls. Half the rabbits of each group were killed 15 days after the first injection of serum. The other half received a second injection of serum 19 days after the first and were sacrificed 5 days later. Three additional rabbits received hyaluronidase only (6000 T.R.U. per kg twice daily by intravenous

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* Saline suspension of Cortone Acetate, Merck.

† Cortate, oil solution. We are indebted to the Schering Corp. for furnishing some of this material.

‡ Micronized aqueous suspension of 21-acetoxypregnenolone, Wyeth.

§ Hydase, Wyeth.