of marked diaphoresis, weakness, loss of consciousness, rapid thready pulse, faint heart sounds, and peripheral vascular collapse were encountered in 3 patients, (Cases 8, 9 and 10) within 5 minutes following the 40th, 53rd and 29th doses, respectively, of the enzyme. Prompt use of artificial respiration, epinephrine intramuscularly, oxygen inhalations and intravenous saline probably prevented fatal termination of these anaphylactoid reactions in patients apparently sensitized by previous injections of the protein enzyme. Another patient (Case 6) had a similar but less severe reaction with spontaneous recovery after the 22nd dose.

Further trial of chymotrypsin was discontinued, not only because it had no effect whatsoever in 10 patients with advanced malignant neoplasms, but because repeated administrations of the protein enzyme are of definite serious hazard.

Summary. Parenteral injections of chymotrypsin had no effect on the course of 10 cases of neoplastic disease in man.

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17152. Ineffectiveness of Chymotrypsin Therapy in Malignancy.*

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An elaborate theory has been proposed by Krebs and co-workers[1,2] which assumes that the cancer cell and the trophoblast cell are fundamentally alike, and that both are destroyed selectively by the pancreatic enzyme chymotrypsin. On the basis of this reasoning, but with few supporting facts, chymotrypsin has been suggested as the palliative of choice in neoplastic disease. This report summarizes the negative results of chymotrypsin therapy in experimental and clinical cancer.

Experimental cancer. The toxic dose of crystalline chymotrypsin† in mice subjected to repeated daily intraperitoneal injection was established at 40 to 80 mg per kilo of body weight. The dose used in treatment was 2.0 mg per kilo, which is 5 times the recommended dose for humans. Forty mice with subcutaneously transplanted sarcoma 180 and 40 without tumor were employed in the experiment. Half of each group received chymotrypsin intraperitoneally 7 days a week for 14 days, the remainder serving as controls. Weight gains were uniform in all 4 groups of animals. Treatment was begun when tumors were measurable, on the fifth day after transplantation, and tumor size was recorded on alternate days thereafter. The average increase in tumor area at the conclusion of the experiment was 3.8 times in the treated animals and 3.7 times in the controls. No change in chymotrypsin inhibitor concentration of the blood as determined by the method of West and Hilliard[3] resulted from the treatment in either normal or tumor-bearing animals.

Clinical Cancer. All patients selected for chymotrypsin treatment had received the maximum benefit from accepted forms of therapy but still had active disease. Their clinical course was followed by an impartial group of observers, Drs. G. M. Leiby, J. A. Weinberg, F. Isaac, and F. W. Wilkins of this hospital. Weekly laboratory determinations included,

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1 Gurchot, C., Krebs, E. T., Jr., and Krebs, E. T., *Surg., Gynec. and Obst.*, 1947, **84**, 301.

2 Krebs, E. T., Krebs, E. T., Jr., and Gurchot, C., *M. Rec.*, 1947, **160**, 479.

† Crystalline Chymotrypsin was supplied by Spicer-Gerhart Co., Pasadena, Calif., and Worthington Biochemical Laboratory, Freehold, N. J.

3 West, P. M., and Hilliard, Jessamine, in press.

blood count, sedimentation rate, bleeding and coagulation time, serum protein, alkaline phosphatase, cephalin flocculation, thymol turbidity, NPN, and serum chymotrypsin and rennin inhibitors.[3] When feasible, patients were followed roentgenographically as well.

The diagnosis in each instance had been proved by biopsy. There were 15 cases in the series: bronchogenic carcinoma, 3; carcinoma of stomach, 2; embryonal carcinoma of testicle, 2; and one each of recto-sigmoid and uterine carcinoma, synovioma, lymphosarcoma, Hodgkin's disease, acute and subacute lymphatic leukemias, and chronic myelogenous leukemia.

Crystalline chymotrypsin in saline was given in daily intramuscular doses ranging from 4 to 60 mg for periods of 21 to 135 days, with an average of 64 days. The usual dose was the recommended one of 30 mg. Three patients could not tolerate more than 4 to 6 mg without intense pain in the most involved organ (liver, stomach and spleen) accompanied by chills and fever 12 to 24 hours after injection. Six cases developed pronounced allergy to the drug, forcing reduction in dose or discontinuation of treatment. Two had generalized urticarial reactions, 2 exhibited anaphylactic shock, and 2 had extreme local erythema and edema at the site of injection. Two patients died in congestive failure about a week after onset of precordial pain, ankle edema and dyspnea. Electrocardiograms were normal before death and autopsy failed to reveal significant cardiac pathology. Whether or not these deaths were related to treatment is debatable.

The sedimentation rate was doubled during chymotrypsin therapy. There were no other consistent laboratory findings. The serum level of chymotrypsin inhibitor was not altered detectably, which is understandable in view of the fact that there is sufficient inhibitor in the circulation alone in many such patients to inactivate 25 to 50 g of pure chymotrypsin.

In no case was the clinical course of the patient influenced by chymotrypsin therapy. Nine patients have died and a study of autopsy material has not revealed any unusual degenerative changes in the neoplasm.

Summary. Treatment with crystalline chymotrypsin did not influence the course of neoplastic disease in experimental animals or in fifteen selected cancer patients.

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17153. Action of Chloromycetin on Salmonella.

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As yet there exists no effective remedy to prevent or cure Salmonella infections in man and animals. Any new antibiotic with selective activity against gram negative organisms, therefore, is worth a trial against Salmonella infections. Chloromycetin, the antibiotic produced by Streptomyces Venezuelae[1] possesses these qualities in addition to its marked effect against Rickettsia. Clinical experiments indicate some success in the treatment of human typhoid fever (a Salmonellosis.)[2]

In vitro tests with a number of gram negative bacilli were performed by Smith *et al.*,[3] and revealed remarkable sensitivity, usually in a range below 1 μg of the drug. These results were obtained by a special turbidity assay method developed by Joslyn and Gal-

[1] Ehrlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., and Burkholder, P. R., *Science*, 1947, **106**, 417.

[2] Woodward, T. E., Smadel, J. E., Ley, H. L., Jr., Green, R., and Mankikar, D. S., *Ann. Int. Med.*, 1948, **29**, 131.

[3] Smith, R. M., Joslyn, D. A., Gruhzit, O. M., McLean, I. W., Jr., Penner, M. A., and Ehrlich, J., *J. Bact.*, 1948, **55**, 425.