with skin from the Cb strain, the other parent strain of the F_1 marrow donor. Of a group of 13 untreated CBA mice simultaneously autografted as controls, 12 of the autografts took. All of the homografts sloughed at the 0, 110 and 330 r dose levels. Of the 11 mice at 770 r that survived skin grafting, all of the foreign skin grafts were accepted and are in good condition 124 to 130 days after grafting. In previous experiments no late sloughs have been observed under similar conditions. Fifteen of 18 grafts at 660 and 770 r were successful and are still in good condition 130 to 152 days after grafting (Experiment B of Table II). In this earlier experiment it will be noted that late mortality in F_1 marrow protected mice at 660 r was greater than at 770 r. In both of these experiments mice receiving the different doses of irradiation were caged separately, 6 to a pen. It is therefore possible that an undetected infectious agent may have involved the 4 pens of mice at 550 and 660 r to account for the greater mortality at these levels than at 770 r. To control this possibility another experiment was set up in which mice receiving 330, 550 and 770 r followed by Cb x CBA marrow were caged together, 2 at each dose level in each pen of 6 mice. Again the mice at 550 r showed much higher mortality than their cage mates at 330 and 770 r (Table III). Body weight loss at 550 r was much greater and more progressive than at 770 r. Blood counts performed 2 weeks post-irradiation showed a significantly lower white and red cell count in the mice at 550 r than in those at 770 r. Platelets were less numerous in the stained blood smears of the mice at 550 r than in those at 770 r.

Discussion. The blood count data suggest that the greater mortality at 550 r than at 770 r may be related to a less adequate hematopoietic recovery. On the other hand, 550 r without bone marrow had earlier resulted in 30-day mortality of only 12% of 24 CBA mice and 9% of 54 mice of all strains combined. Additional experiments are obviously indicated, and no explanation of the mechanism involved will be ventured at this time.

Summary. The 21-day LD_{50} under the conditions of X-irradiation used is approximately 600 r. Irradiation of CBA mice followed by intravenous administration of bone marrow suspension from Cb x CBA F_1 hybrids resulted in little or no 21-day mortality at 110, 330, 660 and 770 r, but in almost 100% mortality at 550 r. Homografts of Cb skin into the surviving mice were accepted by the mice at 660 and 770 r dose levels but not by mice at 0, 110 and 330 r dose levels. None of the marrow-treated mice at 550 r survived long enough to be skin grafted.

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Effect of Chlorpromazine on Excretion of 5-Hydroxyindoleacetic Acid in a Patient with Malignant Carcinoid. (22675)

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Since the first authentic case report of Beger(1) in 1882 of a carcinoid of the appendix the tumor has been of interest to the clinician principally because of its rarity and to the histologist because of its unusual cell type and staining properties. Gosset and Masson(2), using silver impregnation technics, demonstrated the presence of intracytoplasmic granules which stain black with silver and which were indistinguishable from the granules found in the argentaffin cells of the intestinal mucosa. Masson suggested the possibility that carcinoid tumors arise from the argentaffin cells and postulated that the

normal cells had a neuroendocrine function.

Lembeck(3) demonstrated the presence of 5-hydroxytryptamine (5-HT) in carcinoid tumors in large quantities. This observation has led Thorson(4) to suggest that the secretion of 5-hydroxytryptamine (serotonin) by the tumor might serve to explain the unusual symptom complex seen in patients harboring this tumor. The clinical syndrome is characterized by intestinal hypermotility, bronchospasm, vasomotor disturbances and valvular disease of the heart. The recent report of Sjoerdsma(5) *et al.* concerning their investigation on a group of patients with malignant carcinoids support the postulate that the symptom complex described by Thorson and others is due to excess serotonin produced by the tumor. Further studies by the group have shown that 5-hydroxyindoleacetic acid (5-HIAA) is formed by oxidative deamination of serotonin and excreted in the urine(6). Increased amounts of this metabolite have been demonstrated in the urine of patients with malignant carcinoid and a method for its assay has been described by Udenfriend(7). The recent reports of Benditt(8) showing antagonism of 5-HT by chlorpromazine led us to study the effects of this drug on a patient with a known malignant carcinoid.

Method. The patient was a 56-year-old white woman in whom a carcinoid tumor of the ileum was diagnosed and resected in 1950. At the time of laparotomy metastases of the tumor to regional lymph nodes and liver were observed grossly and confirmed microscopically. She has enjoyed reasonably good health since that time with the exception of chronic diarrhea, occasional episodes of "flushing" and periodic exacerbations of "arthritis." No cardiac abnormalities have been noted. The patient was admitted to the Metabolic Division of University Hospitals and placed on a constant diet which remained unchanged during the study period. All urine was collected and aliquots from each 24-hour period were placed in a deep freeze. The number and character of the bowel movements were recorded for each 24 hours. Following a control period of 5½ days the patient was started on oral chlorpromazine,* 25 mg every 6 hours. This was continued for 4 days at which time the drug was discontinued. The observation period extended for an additional 4½ days following withdrawal of the medication. The 24-hour urine samples were assayed for 5-HIAA according to the simplified method of Sjoerdsma *et al.*(9). A gross quantitation of the amount of 5-HIAA excreted was made by the intensity of the color produced by the test and was adequate for our purpose. The patient received no other medication during the experimental period.

Results. Following administration of chlorpromazine there was a prompt and marked decrease in the excretion of 5-HIAA in the urine and a decrease in the number of bowel movements per 24 hours (Fig. 1). The stools became semi-solid in contrast to watery bowel movements observed during the control period. Within 24 hours following discontinuation of the medication the urine 5-HIAA content returned to control levels and the diarrhea again became manifest after 72 hours.

Discussion. The evidence that carcinoid tumors produce excess quantities of serotonin seems incontrovertible and patients with this lesion afford an unusual opportunity to study the pharmacodynamic effects of this substance *in vivo*. The patient described in this study may be added to a growing list of reported cases in whom the presence of this tumor is associated with unusual clinical manifestations which may be attributable to serotonin excess, *i.e.*, diarrhea, vasomotor disturbances (flushing), etc. The antagonistic effect of chlorpromazine on serotonin previously demonstrated in experimental animals(8) is further supported by this study as shown by the decrease in urinary 5-HIAA following administration of the drug. The decrease in intestinal hypermotility as manifested by the reduction in the number of stools noted in this patient affords additional corroborative evidence of serotonin inhibition. The mode of action of serotonin inhibition by chlorpromazine remains speculative. It is not to be inferred from this report that chlorpromazine is necessarily recommended in the clinical management of these patients albeit true that symptomatic relief of the distressing diarrhea

* Thorazine—Smith, Kline and French.

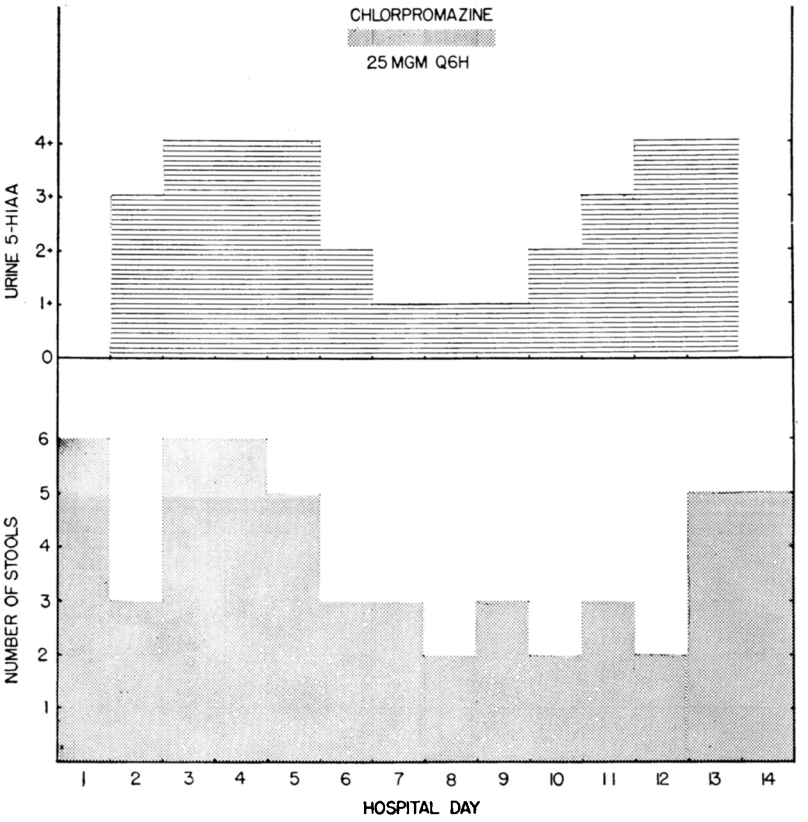

FIG. 1. Graph showing prompt fall in the urine 5-hydroxyindoleacetic acid following oral administration of chlorpromazine and a return to premedication levels following withdrawal of the medication. Concomitant diminution in the No. of stools is also depicted occurring with chlorpromazine medication.

was observed.

Summary. 1. A marked fall in urinary 5-HIAA excretion followed administration of chlorpromazine to a patient with known malignant carcinoid. 2. Intestinal hypermotility, one manifestation of the so-called "carcinoid syndrome" was likewise suppressed during administration of the drug.

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