Bronchial Adenoma and the Carcinoid Syndrome

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Primary carcinoid tumors usually occur in the bowel, especially in the ileocecal region. These neoplasms may also be found in the bronchus and mediastinum and in such uncommon sites as pancreas, stomach, gallbladder, parotid gland, testis, and retroperitoneal space.[14, 31, 35, 43] Although carcinoid tumors are not unusual, the associated carcinoid syndrome is encountered less frequently.

Tumors of the carcinoid type originate from argentaffin cells. The oncogenesis of bronchial carcinoid lesions has been related to oncocytes, bronchial buds, bronchial counterparts of the intestinal argentaffin cell, and bronchial glands. Using the electron microscope, Bensch[5] described bronchial carcinoid as distinctive and resembling neuroblastoma, carotid body tumor, adrenal medulla, and especially Kulchitsky's cell. The cell of origin appeared as a normal but scant component of bronchial glands, identical with the intestinal argentaffin cell.

The carcinoid syndrome may include a wide variety of disorders. Some symptoms may be episodic, transitory, and varying in intensity and duration, while others may be continuous and the result of permanently altered physiology. Some patients with functioning tumors may not have the syndrome. Episodic phenomena include the characteristic flushing with a dusky red hyperemia over the neck, chest, and arms; sweating; tachycardia; pruritus, paresthesia; edema of the face and hands; and occasionally vasomotor collapse. Other symptoms include asthma, hyperperistalsis, and diarrhea. Manifestations that may become permanent are facial hyperemia with edema of the hands and face, and valvular heart disease.

Several explanations for the pathophysiology of the syndrome have been proposed. Hyperemia has been attributed to (1) hyperserotoninemia, (2) the interaction of histamine and serotonin, (3) the interaction of catecholamines and serotonin, and (4) elevated levels of polypeptide bradykinin in the blood.[10] Because there may be poor correlation between the concentration of hemic serotonin and the carcinoid syndrome some persons with elevated serotonin levels may have no symptoms. Warner, Kirschner and Warner[48] report that bronchial adenomas may produce hyperserotoninemia in the absence of symptoms or metastases. However, the syndrome has been associated with tumors which do not produce serotonin but secrete large amounts of 5-hydroxytryptophan, probably because of absence of decarboxylase in the tumor.[9, 31, 36] Schneckloth, McIsaac and Page[38] reported an unidentified 5-hydroxyindole which was elevated more than serotonin in one patient. Generally, bronchial carcinoid lesions contain less serotonin than those in the ileum.[50] It has been postulated that the essential change produced by the carcinoid tumor is a quantitative disturbance in metabolism of the amino acid

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tryptophan in the production of serotonin and metabolism to 5-hydroxyindole acetic acid (5-HIAA). Normally, about 1 per cent of the dietary tryptophan enters the serotonin pathway. In the carcinoid syndrome, some 60 per cent may be metabolized in this manner.[41] Bronchial carcinoids may have the malignant potential and capacity for excessive secretion of serotonin as do similar lesions in the small bowel.

In 1957, a case of the carcinoid syndrome associated with an "oat cell" carcinoma of the lung was reported;[19] and the first cases of bronchial carcinoid and the carcinoid syndrome were reported in 1958.[15, 28, 37, 44, 47] Although approximately 85 per cent of bronchial adenomas are of the carcinoid type[22] only a few are endocrine-functioning with production of the carcinoid syndrome.[20]

In 1964, Askergren and Hillenius[2] reported one case of bronchial adenoma associated with the carcinoid syndrome and reviewed 26 previously recorded cases. Subsequently in 1966, Melmon, Sjoerdsma and Mason[26] reported three cases and discovered three additional cases in the literature.[6, 7, 17] Two cases (one definite and one probable) were added in 1966 by Batson, Gale and Hickey.[4] In these 35 cases, the sex distribution was essentially equal, and the average age was approximately 48 years. Most patients had two or more cardinal symptoms. Urinary 5-HIAA had increased to pathologic levels, and the typical flush was present in 19 of the 25 patients in whom it was mentioned. The flush often was more pronounced and prolonged than that in carcinoid lesions in the intestines. The severity of the disease and the amount of 5-HIAA which was excreted did not seem related. Some patients had the fully developed syndrome with only slightly elevated serotonin levels. Conversely, other patients did not have symptoms although excretion of 5-HIAA was excessive.

Many patients with bronchial carcinoid tumors develop metastases. Goodner, Berg and Watson[18] reported metastases in 44 per cent of patients—with a 5-year-survival rate of only 57 per cent. However, these lesions grow slowly and some have been observed for at least 9 years before evidence of dissemination. Until 1960, metastasis to the liver was considered essential in the production of the carcinoid syndrome. In that year, Joseph and Taylor[22] reported a case of bronchial carcinoid tumor and associated carcinoid syndrome. Their patient had no metastases to the liver as proved at autopsy. Interestingly, all reported bronchial carcinoid tumors with associated skeletal metastases have been of the osteoblastic type,[21] but an adequate explanation for this predilection has not been presented. In three patients, positive evidence of endocardial fibrosis was found only in the right side of the heart.[1, 3, 49] All of these patients had rapid downhill courses, all expired within two years, and in all metastases to the liver were proved. Approximately 40 per cent of patients with carcinoid tumors originating in the small intestine develop endocardial fibrosis (a late but frequent complication). Because the route of venous return from a bronchial carcinoid tumor is primarily to the left auricle, it would seem that endocardial fibrosis should develop in the left side of the heart; however, only a few such cases have been reported.[6, 24, 26] This phenomenon provides additional evidence that factors other than hyperserotoninemia must be operating to produce the carcinoid syndrome. Serotonin is eliminated primarily in the liver and in the lungs. To explain the development of endocardial fibrosis in the right but not in the left side of the heart would be difficult unless areas of extraportal metastases excrete considerably larger amounts of serotonin than does the primary tumor. That endocardial fibrosis in the left side of the heart accompanies carcinoid lesions in the intestine only when the right side of the heart is involved suggests that the primary tumor and its extra-

portal metastases excrete serotonin in such amounts that all of it cannot be eliminated in the liver or lungs.[49]

Detection of excessive excretion of 5-HIAA in the urine is the most valuable laboratory evidence of a functioning carcinoid tumor. However, as indicated previously, hyperserotoninemia may be present without the syndrome, and the syndrome may occur in patients who excrete normal amounts of 5-HIAA (from 2 to 8 mg. in 24 hours). Generally, there is a significant increase of 5-HIAA excretion when the syndrome is present. Daily excretion of more than 25 mg. of 5-HIAA has been considered diagnostic of the carcinoid syndrome; however, most patients with the syndrome excrete more than 100 mg. in 24 hours.[42] Often the cause of death in this disease is cardiac failure secondary to a valvular lesion.[40]

Treatment

The carcinoid syndrome is a biochemical complex usually due to metastases. Extirpation of all tumor tissue is rarely possible. Therefore, treatment must be directed toward reduction of the tumor mass by resection, irradiation, or chemotherapy to bring about a parallel reduction in biochemical agents. If this therapy proves ineffective, treatment with chemical antagonists to the metabolic products of the tumor must be considered.

Surgical Management. Because the urinary biochemical abnormality must be present for a prolonged period to produce a carcinoid syndrome, aggressive palliative surgical treatment is indicated if the neoplasm is resectable and if the patient's condition permits. Metastases usually produce serotonin or other biologically active substances, and the symptoms ordinarily are proportionate to this hyperserotoninemia. Usually, however, the severity of the syndrome can be decreased by reducing this excessive secretion.

If the metastatic lesions are accessible, total removal of all neoplasia should be attempted. If metastases involve the liver and carcinoid syndrome is associated, resection of the involved hepatic tissue may be indicated. Even when all lesions cannot be removed, decreasing the total tumor mass will effect significant clinical improvement. Heart failure may be an important indication for removal of anatomically accessible hepatic metastases.[29] Photoscanning is valuable for determining the feasibility of resecting metastatic lesions of the liver. Extension to mediastinal lymph nodes secondary to a bronchial lesion should also be excised. Because the tumor grows slowly, palliation may be effective for months or years.

Because of increased sensitivity to anesthetic agents, the danger of operation is increased in the carcinoid syndrome.[27] Carcinoid crises, with severe hypotension and flushing, may occur during induction of anesthesia. Hypotension induces serotonin release, especially if the onset is abrupt. Mengel[28] suggested that antiserotonin compounds be administered before and during operation, and Stone and Donnelly[45] recommend that spinal or epidural anesthesia as well as rapid thiopental induction be avoided. It is important to treat hypotensive episodes with methoxamine rather than with vasopressor agents because norepinephrine, epinephrine, and esoproterenol induce carcinoid reactions when administered intravenously. Methoxamine infusions cause only minor, if any, flush reactions.

Chemotherapy. Drugs effective in the treatment of the metastatic carcinoid syndrome are cytotoxins and pharmacologic antagonists.

Cytotoxins. Minimal information has been accumulated concerning the response of patients with bronchial carcinoid tumors to chemotherapy. Dollinger and Gardner[16] reviewed the value of cytotoxic agents in metastatic carcinoid syndromes other than those associated with bronchial

adenomas. The best results have been reported with cyclophosphamide. (Mengel[28] reported objective regression of tumors in four of eight patients, and Reed and associates[32] reported seven objective remissions in 15 patients.) Two other alkylating agents, nitrogen mustard[46] and thio-tepa,[32] have been beneficial, while a fourth alkylating agent, phenylalanine mustard,[34] was not effective. The antimetabolic, 5-flououracil (5-FU), was reported to bring about "partial response" in three of seven patients.[34] Reed and coworkers,[32] however, reported objective regression of the tumor mass when 5-FU was introduced intra-arterially through a catheter in the hepatic artery.* Although these carcinoid syndromes did not arise from bronchial adenomas, the method of therapy would be as applicable to metastatic bronchial carcinoid tumors as to those arising from other sites.

Surgical excision should be the primary therapy in resectable carcinoid lesions, leaving the cytotoxic agents for secondary measures when removal of neoplastic tissue is not feasible. A cytotoxic agent should be tried at some time during the course of the disease. Although response may be only transient, some objective remissions persisted for one or more years.

Pharmacologic Antagonists. All patients with bronchial adenomas and the carcinoid syndrome are not suitable for surgical resection or cytotoxic therapy. At some time, the lesions are no longer resectable or the patient fails to respond to chemotherapy. Pharmacologic antagonists may be useful in such instances.

Serotonin Antagonists. Because, initially, the symptoms of the carcinoid syndrome were considered due to excessive serotonin, therapeutic attempts have been made to block its formation or its physiologic effect. Dietary restriction of pyridoxine and pyridoxine analogues such as desoxypyridoxine have been tried somewhat unsuccessfully.[39] Isonicotinic acid hydrazine proved impractical.[16] Alpha-methyl-dihydroxyphenylalanine, an agent blocking conversion of 5-hydroxytryptophan to serotonin, proved relatively ineffective except in patients with metastatic gastric carcinoid lesions.[11, 12, 30] Methysergide maleate and cyproheptadine have been used extensively with variable results.[16] Although results are unpredictable, serotonin antagonists deserve a therapeutic trial, especially if flush and diarrhea are severe. These agents produced dramatic results in some patients.

Tryptophan Antagonists. In 1965, Costello[13] reported 12 patients who were treated with various tryptophan analogues in an effort to reduce intracellular metabolism of metastatic carcinoid tissue and thus reduce symptoms due to metabolic products. He reported that the halogenated tryptophan analogues most consistently control flushing and diarrhea; but that, during treatment, while some patients had metastatic lesions enlarge they showed subjective clinical improvement.[13]

Kinin Antagonists. Kinin antagonists have been suggested as playing a role in the metastatic carcinoid syndrome and chlorpromazine is considered of value in controlling symptoms. Recently Rocha e Silva[33] suggested that chlorpromazine may be effective as a peripheral blocking agent as well as a tissue antimetabolite. Also the kallikrein inhibitor, trasylol, has been used in the carcinoid syndrome.[16] Although, this drug proved ineffective in one instance, the level of kinin was not elevated in the patient.

Adrenocortical Hormones. Adrenocortical hormones have been reported beneficial, in carcinoid syndrome particularly when due to bronchial tumors. Melmon, Sjoerdsma and Mason[26] stated that steroids were "life-saving" in a patient with metastatic carcinoid syndrome, considerably reducing symptoms for more than a year. Three pa-

* This therapy is applicable only if the liver is the principal site of metastasis.

tients showed some response to this therapy, two having dramatic relief with some objective change in the tumor mass.[26]

The mechanism of response to adrenocortical hormones has not been explained, but immunosuppression in symptoms resembling an allergic reaction is an intriguing consideration. In a report by Levine and Sjoerdsma,[25] allergic factors were strongly implicated and one patient responded promptly to adrenocorticotrophin hormone (ACTH).

Irradiation Therapy. Irradiation has had variable results in the malignant carcinoid syndrome. Brown, Bissonnette and Steele[8] administered 3,000 r to a patient with lymph node metastases without significant response. Mengel[27] noted a decrease in the size of the liver, lowering of the level of serotonin in the blood, and a transient increase in 5-hydroxy-3-indole acetic acid in the urine after irradiation therapy. These biochemical changes were attributed to tumor destruction. Sauer, Dearing and

TABLE 1. *Carcinoid Tumors of the Bronchus*

Case	Type Tumor	Metastases	Associated with Syndrome	Treatment	Follow Up
1	Solid type carcinoid	Mediastinal lymph nodes	No	Pneumonectomy Lymphadenectomy	Died 7 weeks P.O. Coronary infarction
2	Solid type carcinoid	Extensive lymph node & mediastinal metastases	No	Exploratory thoracotomy; Biopsy; nitrogen mustard & x-ray therapy	No follow up
3	Trabecular carcinoid with extension through the bronchus	No	No	Pneumonectomy	Alive and well, 3½ years P.O.
4	Trabecular carcinoid	No	No	Lobectomy	Alive and well 5½ years P.O.
5	Solid type	No	No	Pneumonectomy	Alive and well 9 years P.O.
6	Solid type	No	No	Segmental Lobectomy	Alive and well 10½ years P.O.
7	Solid type	No clinical metastasis	No	Refused surgery	No follow up
8	Solid type	No	No	Pneumonectomy	Alive and well 13 years P.O.
9	Solid type	No	No	Lobectomy	Alive and well 2½ years P.O.
10	Trabecular type	No	No	Lobectomy	Alive and well 13 years P.O.
11	Solid type	No	No	Pneumonectomy	Alive and well 15 years P.O.
12	Solid type	No	No	Lobectomy	Alive and well 3 months P.O.
13	Solid type	No	No	Lobectomy	Alive and well 6 months P.O.
14*	Solid type	None in chest Liver metastasis 8 months P.O.	Yes	Lobectomy; 5-FU intra-arterially; sterane; x-ray Cyclophosphamide	Alive with carcinoid syndrome 14 months P.O.

* Case reported in this paper.

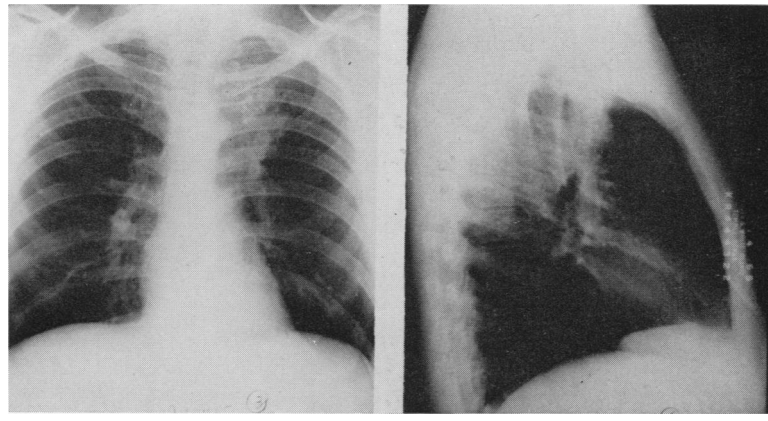

FIG. 1. Roentgenograms of the chest revealing evidence of a tumor in the upper lobe of the left lung.

Flock[87] did not observe any benefit from irradiation therapy.

Scott and White Series

At the Scott and White Clinic, fourteen patients with bronchial adenoma of the carcinoid type were seen during the 15-year-period from 1950 to 1966. Eleven were of the solid carcinoid variety and three had a primary trabecular pattern. None of the tumors were the cylindromatous or mucoepidermoid type. Thirteen of the fourteen patients had surgical treatment. Table 1 indicates the nature of the lesions, treatments, and subsequent results. Only one patient had bronchial adenoma associated with the carcinoid syndrome.

Case Report

On July 13, 1965, a 49-year-old man reported to the Scott and White Clinic for clinical investigation. Hemoptysis of five months' duration and mild digestive upsets were his chief complaints. Results of physical examination, routine laboratory tests, and roentgenograms of the gallbladder, esophagus, stomach, and colon were normal. Proctoscopy revealed a lesion in the sigmoid colon which on removal was a benign adenomatous polyp. Roentgenograms of the chest showed a lesion in the upper lobe of the left lung (Fig. 1). (On review of previous roentgenograms a small lesion was visible in this same area in 1964, and it had become larger in 1964 and in 1965 (Fig. 2).) Serologic tests were negative for syphilis; and the coccidioidin, histoplasmin, and tuberculin skin tests were negative.

Bronchoscopy and biopsy of left cervical paratracheal lymph nodes were performed on July 20, 1965. Mild bronchitis was the only reported abnormality, and the lymph nodes showed mild inflammatory changes. Bronchial aspirations and sputum samples contained the usual bacterial flora with no evidence of neoplasm, tuberculosis, or fungal disease. Bronchogram of the left lung showed elevation of the left main bronchus without filling of the apicoposterior segment of the left upper lobe, and the superior division of the left lower lobe was displaced upward. Planigrams confirmed the presence of a tumor (Fig. 3). Left exploratory thoracotomy was advised, but the pa-

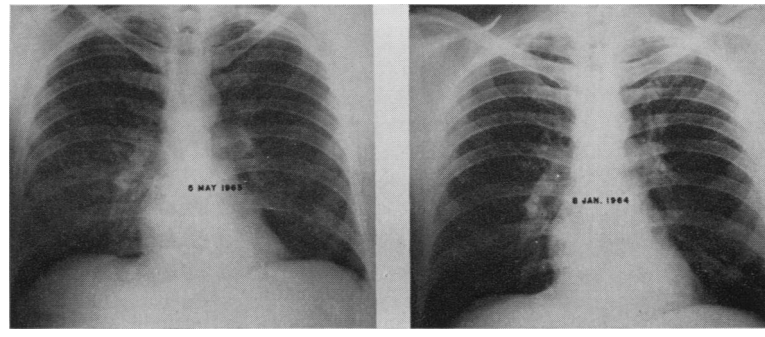

FIG. 2. a. Roentgenographic evidence of pneumonitis in the area of the tumor as early as May 1963. b. Comparative roentgenogram (January 1964) demonstrating that the density had increased.

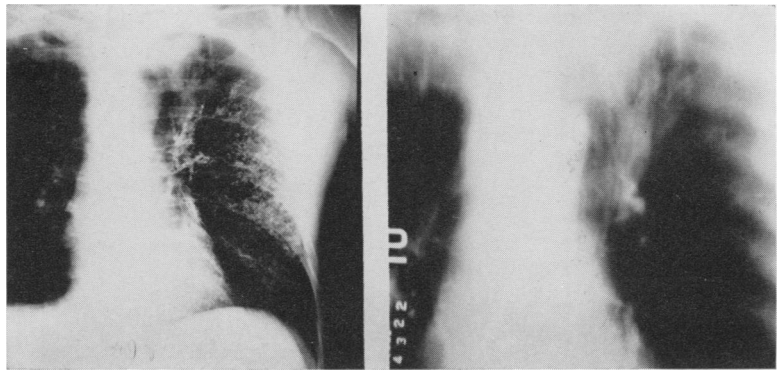

FIG. 3. a. Bronchogram demonstrating elevation of the left main bronchus with absence of filling of the apicoposterior segment of the left upper lobe. b. Planogram showing the lesion in the left apex.

tient deferred this operation. One month later, the only new symptom was occasional sweating at night. On deep inspiration, the liver descended 2 to 3 cm. below the right costal margin.

On August 24, 1965, through a left posterolateral thoracotomy, a large tumor was found in the upper lobe of the left lung. The mass extended onto the pleura, and there were numerous adhesions in the apex of the left hemithorax. One enlarged node in the mediastinum was removed for microscopic examination. Also, the mass in the lung was biopsied. Both specimens were reported benign. Left upper lobectomy, apical pleurectomy, and upper mediastinal lymphadenectomy were performed. The surgical specimen contained an adenocarcinoma, Grade I (bronchial adenoma) in the upper lobe of the left lung with an abscess distal to the neoplasm. Metastases to the lymph nodes were not seen.

The patient's convalescence after lobectomy was uncomplicated. When he returned 2 months later, a moderate flushing of his face and neck, fever to 38.5° C., and occasional slight wheezing after drinking one or two bottles of beer had developed. Physically, he was normal except for the reddish purple flushing and temperature of 37° C. While carcinoid syndrome was suspected, a scanogram of the liver was interpreted as "normal," tests for urinary 5-HIAA were negative, and sedimentation rate was 21 mm. in one hour (Westergren method).

The patient returned on April 20, 1966, 8 months after lobectomy, stating that he remained flushed most of the time and occasionally would have fever 39° C. (Fig. 4). Urine samples now contained 5-HIAA in 1:50 dilution. Needle biopsies of the liver were normal, but a scanogram suggested multiple small metastatic areas. Prothrombin time was 100%, and the sedimentation rate was 7 mm. in one hour (Westergren method). Routine blood tests, chest and colon roentgenograms, proctoscopic examination, electrocardiograms, and urinalysis were normal.

With percutaneous right transfemoral catheterization of the celiac artery on April 27, and subsequent continuous intra-arterial infusion of 5-FU (2 Gm./24 hr.) for 10 consecutive days, his flush decreased, and he felt improved. This amelioration lasted three months until July, when he developed diarrhea, lost weight, and flushing and fever increased. The liver extended 3 cm. below the right costal margin and 8 cm. below the xiphoid process. The flush discoloration now covered his face, neck, chest, and abdomen. Laboratory data included scanographic evidence of in-

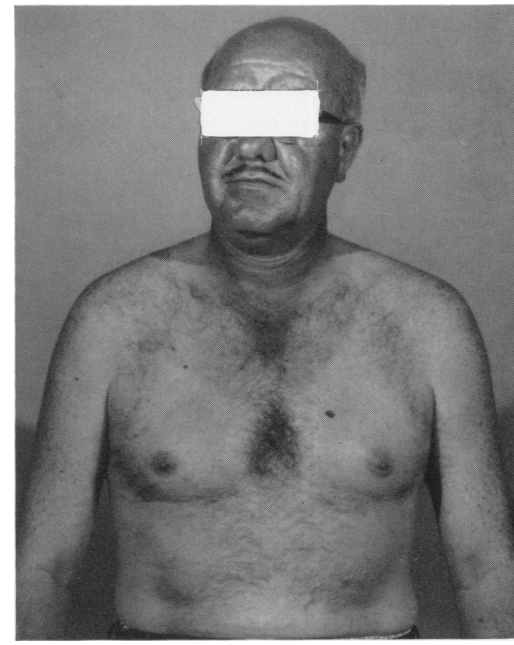

FIG. 4. Photograph of patient showing the typical carcinoid flush present eight months after lobectomy.

creasing metastases in the liver; sedimentation rates elevated to 67 mm. and later to 78 mm. (Westergren method); 163 mg. of 5-HIAA excreted per 24 hours in the urine; the SGOT 8 units; urinalyses showed grade III albuminuria, grade II hematuria, and occasional granular casts; blood urea was 17 mg./100 ml.; and urine cultures were negative. Roentgenographically, the chest remained essentially normal (Fig. 5). With prednisolone (10 mg., 4 times daily) and hydroxyzine, flushing decreased and diarrhea was controlled. The liver measured 4 cm. at the right costal margin and 11 cm. at the xiphoid process, indicating progression of the hepatic metastases.

Subjective improvement was short-lived. The liver continued to enlarge. One month after adrenocortical therapy was begun, diarrhea returned, the flushing became severe, and the patient became extremely depressed. At this time, the liver was 7 cm. at the right costal margin mid-clavicular line and 11 cm. at the xiphoid process. Erythrocyte sedimentation rate had decreased to 33 mm./hr. Excretion of 5-HIAA in the urine was 301 mg. in 24 hours. The patient was given cyclophosphamide (500 mg., intravenously on 5 consecutive days), and irradiation therapy to the liver (3,000 r. from a 6 MEV course).

At the time irradiation therapy was completed on October 24, the adrenocortical hormones had been discontinued. The patient had much less flushing, but the liver had not decreased in size. Diarrhea was controlled 6 days after cyclophosphamide regimen had been completed. Urine was negative for 5-HIAA.

Cyclophosphamide therapy was started on October 7. On November 28, he had received four courses (500 mg., intravenously, over 4 to 5 days), a minimum of 2 Gm. for each course. With this medication, 5-HIAA in the urine remained negative. Subjectively, he improved; however, flushing occasionally occurs. Edema and pigmentation of his face remains. The scanogram of the liver showed some diminution of metastases. Evidence of the tumor remains, but activity has been decreased markedly by cyclophosphamide.

Summary

The carcinoid syndrome includes symptoms and signs associated with elevated levels of tryptophan metabolites and one or several biologically active peptides. Primary carcinoid tumors usually occur in the bowel, but may develop in other sites including the bronchus. Although approximately 85 per cent of bronchial adenomas are of the carcinoid type, only a small number are endocrine-functioning. These neoplasms grow very slowly and may be present for years before evidence of dissemination occurs.

Treatment of the carcinoid syndrome is palliative, but suitable measures lessen symptoms for months or years. If hepatic metastases are accessible to excision, surgical removal should be attempted. Because patients usually are sensitive to anesthetic agents, appropriate precautions must be taken in the choice of drugs and in the administration of anesthesia.

When surgical treatment is not possible, chemotherapy should be considered. Objective tumor response has been reported with intravenous cyclophosphamide and intra-arterial (hepatic) 5-flourouracil. Metabolic antagonists have provided varied results. Chlorpromazine, which might act as a bradykinin inhibitor, has been of use symptomatically. Adrenocortical hormones should be tried in patients with marked flushing, fever, and rapid deterioration.

Irradiation therapy has produced vari-

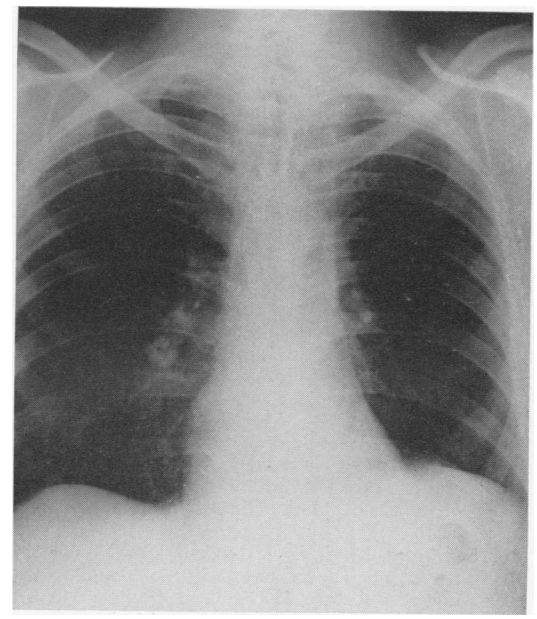

FIG. 5. Essentially normal roentgenogram of the chest nine months after lobectomy.

able results and is not the treatment of choice. At present, optimum palliation is achieved by surgical excision of all accessible metastases and adjunctive chemotherapy for residual functioning lesions.

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Discussion

Dr. Harwell Wilson (Memphis): Dr. Mahorner, gentlemen: I think that all of us will agree that both Dr. Creech and Dr. Brindley have significantly contributed to our better understanding of this relatively poorly understood tumor.

(Slide.) In 1963 we reported our experience with 78 patients with carcinoid tumors found in our teaching hospital over a period of 20 years. In this group of 78 there was only one carcinoid tumor of the stomach and none of the duodenum. This makes Dr. Creech's thesis all the more interesting to us.

There were two patients in this group who had a carcinoid tumor of the bronchus. One of these tumors was obviously malignant; one had the carcinoid syndrome and one did not. Recently another patient on our service was operated upon for a malignant carcinoid of the bronchus by Dr. Paul Sherman, who is here as a guest this morning.

I was especially interested in the report by Dr. Brindley that the patient with liver metastasis had the carcinoid syndrome controlled by chemotherapeutic agents.

(Slide.) A report of this patient with extensive hepatic involvement of the liver secondary to carcinoid of the ileum with severe carcinoid syndrome symptoms was presented to this association at the 1958 meeting. The enlarged liver extended down to the pelvic brim and the disabling carcinoid syndrome symptoms made it necessary for the patient to stop work.

We removed the primary site of the tumor by resecting the terminal ileum and the adjacent mass of lymph nodes which were involved by the tumor.

(Slide.) As can be seen, most of the left lobe and a considerable portion of the right lobe were removed. The amount of liver removed was equal to the weight of a normal liver.

I wish to give a follow-up report on this patient, since as Dr. Brindley stated, regardless of how the patient with liver metastasis is treated the therapy is still only palliative. Our patient was relieved of his carcinoid syndrome symptoms for approximately 5 years. This was associated with a fall in the 5 HIAA level in the urine. When symptoms of the syndrome returned along with recurrent enlargement of the liver a second partial hepatic resection was done and the patient again obtained symptomatic relief from the syndrome.

Dr. William S. McCune (Washington, D. C.): Dr. Mahorner, Fellows and guests of the Association: I have enjoyed both of these papers very much.

I think the paper by Dr. Creech has given us definite evidence of something which we have suspected for some time, namely that both islet cell tumors and carcinoid tumors may be related.

When the carcinoid syndrome was first described by Thorson and co-workers, and when serotonin was discovered in large amounts in extracts of the tumor, we all concluded that this hormone caused the various symptoms of the carcinoid syndrome.