The Syndrome of Carcinoid and Acquired Valve Lesions of the Right Side of the Heart

By William B. Bean, M.D., David Olch, M.D. and Harry B. Weinberg, M.D.

Recent papers by Biöck and Rosenbaum have revived interest in the rare disease characterized pathologically by carcinoid of the small intestine, metastases to the liver, acquired nonrheumatic disease of the tricuspid and pulmonic valve, and angiosarcoma in the skin. Clinically the condition is characterized by dramatic episodes of flushing, mottling of the skin, diarrhea, dyspnea and ultimately by congestive failure. Probably 5-hydroxytryptamine (serotonin) liberated from the carcinoid tumors induces the vascular changes. The suggestion is set forth that an antagonist to this compound might reduce the symptoms and perhaps favorably affect the course of the disease.

Two cases are reported.

ELINEATION of rare syndromes to advance our knowledge of medicine is erratic and may depend on whim or circumstance rather than concerted plan. Nonetheless by unraveling exotic disorders we may get welcome light on seemingly unrelated obscurities. Though rare diseases do not accumulate in large numbers, a lucid paper or a timely talk may catch the attention of many clinicians and what seemed rare is found to be merely uncommon.

Recently there has been a flurry of interest in the strange combination of carcinoid of the small intestine with metastases to the liver; acquired disease of pulmonary and tricuspid valves; and the clinical features of sudden irregular bursts of flushing of the skin with changing mottled cyanosis; diarrhea; "asthma" and finally edema and ascites. This witch's brew of unlikely signs and symptoms, intriguing to the most fastidious connoisseur of clinical esoterica, now has yielded clues which may help illuminate some aspect of valvular disorders of the heart in general.

One of us (W. B. B.) has studied vascular lesions in the skin for many years, as well as certain aspects of induced flushing. Before the recent reports of the carcinoid-cardiac syndrome we had studied a patient who fell into this category and had reviewed related medical reports, many of which have been reviewed. One of us (H. B. W.) had observed another patient. It is our purpose to report these two cases, call attention to reports of other probable ones, and present a suggestion about treatment.

CASE REPORTS

Patient 1. L. R. O. was a 42-year-old white housewife. She was admitted to the Medical Service of the University Hospitals on Aug. 29, 1951 with the main complaint of diarrhea and unusual skin lesions. She had been in good health until 18 months before admission when, rather abruptly, she developed diarrhea with about six loose, watery stools daily. There had been several tarry stools but no fresh blood or mucus. When this trouble was beginning she had generalized abdominal cramps. They lasted for about two weeks and then subsided. The diarrhea persisted. During the year before admission, she noticed recurrent erythema of the skin, diarrhea, dyspnea and finally edema and ascites. She had been studying exotic disorders and what seemed rare is found to be merely uncommon.

From the Department of Medicine and the University Hospital of the College of Medicine, State University of Iowa, Iowa City, Ia.

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skin over the trunk, abdomen and face. The cheeks and bridge of the nose became blotched. There was a bizarre, rapid and unpredictable change in the distribution and indeed the character of the lesions. They were always aggravated by heat or pressure. The skin of the lower abdomen, back and lower extremities was continuously cyanotic. There was progressive weakness. She was tired, had no appetite and at times had nausea. She had no fever or chills but had lost 40 pounds. During the month prior to admission she had persistent nonpitting edema of the ankles. It was reduced, but not eliminated, by mercurial diuretics. She had mild exertional dyspnea during that period.

About six months before admission small petechiae appeared on her arms. They persisted at the time of her admission. There was no history of rheumatic fever or congenital heart disease. She had had grand mal epilepsy for 10 years, well controlled with Dilantin for the past four years. A subtotal hysterectomy had been done 11 years prior to admission for reasons unknown.

Physical examination. The patient was a chronically ill white woman who had lost much weight. She looked her age. The skin underwent rapid and extreme changes during the examination, the like of which none of us had seen before. A recurring alternating pink and erythematous blotchy blush discoloration occurred over the chest, abdomen and back (fig. 1). The changes resembled giant urticaria with geographical outlines but the edges were not raised. A complete transformation in the lesions might occur, a whole new pattern appearing within three to five minutes resembling in clinical miniature the fickle phantasmagory of the Aurora Borealis. The bluish mottling of the trunk and lower extremities remained constant. There were scattered petechiae over the arms and legs. Some of the larger lesions had thick indurated edematous surfaces projecting above the level of the skin.

There was generalized lymphadenopathy affecting mainly cervical, axillary and inguinal nodes which were firm and fixed to the surrounding tissue. Petechiae were noted on the buccal mucosa. The neck veins were distended. They had prominent pulsations. The chest was symmetrical. The lungs were normal. The breasts were atrophic without scars or lumps.

The heart had an overactive right ventricle; the sounds were of good quality; the rhythm regular. The left cardiac border was in the midclavicular line. The second pulmonic was greater than the second aortic sound, and the first apical sound was accentuated. A harsh, blowing systolic murmur was heard to the right of the sternum in the second intercostal space. It was heard well in the pulmonic area and was transmitted to the neck. At the apex there was a systolic murmur and a low pitched rumbling diastolic murmur. Arterial blood pressure was 100/60. The peripheral pulses were palpable. Oscillometric readings were normal.

The abdomen was flat but the liver was palpable in the right upper quadrant extending 5 cm. below the rib margin. The spleen and kidneys were not felt. Vaginal and rectal examinations were not unusual. The test for occult blood in the stool was negative. In addition to the mottled discoloration of the legs, there was 4 plus non-pitting edema of the ankles and legs. The neurological examination was normal.

Laboratory tests yielded these results: the urine had a specific gravity of 1.013 and was negative.

![Fig. 1. Color photographs of the flushing taken one minute apart.](http://circ.ahajournals.org/content/54/2/2167.full.pdf)
The hemoglobin was 12 Gm., red blood cell count 4.3 million, and the white cell count was 7,350 with 54 per cent neutrophils, 38 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. Serologic test for syphilis was negative. The sedimentation rate was 7 mm. in 1 hour (Westergren). Bleeding time was 1 minute. Coagulation time was 4 minutes. Clot retraction was complete. Prothrombin time was 15.5 seconds with a control of 15.5. The platelet count was 130,000. The serum proteins were 6.16 Gm. per 100 cc. with 3.86 Gm. of albumin and 2.3 Gm. of globulin. The cephalin flocculation test was negative at 24 and 48 hours. Bromsulfalein retention was 2 per cent at the end of 45 minutes. The Rumple-Leeds test was negative. Spinal fluid dynamics and chemical tests were normal.

Fluoroscopic examination of the heart showed definite right ventricular in- and outflow path enlargement without demonstrable left auricular enlargement. Films and fluoroscopic study of the colon with barium showed decrease in haustral markings and slight serration in the sigmoid portion. Upper gastrointestinal x-ray studies, skull films and pneumoencephalogram were negative. The electrocardiogram was normal. One of the petechiae removed from the right deltoid region revealed patchy perivascular edema and lymphocytic infiltration into the blood vessels of the derma (fig. 1) The epidermis and dermal adnexae were normal. The muscle itself was normal. Sternal bone marrow was hypocellular. There were no lupus erythematosus cells.

Routine agglutinations for brucellosis, typhoid fever and paratyphoid were negative. Complement fixation test for amebiasis was positive. No ova or parasites could be found in the stool and the sigmoidoscopic examination was normal. Nonetheless she was given a course of antiamebic therapy with Diodoquine and Chloroquine. No improvement occurred.

She left the hospital unimproved, undiagnosed and untreated. Her continually declining health caused her to enter the hospital in her home town where skin biopsy was repeated with the same findings. A lymph node from the right inguinal region showed calcification. Tests for hemochromatosis were negative. Serum calcium was 14 mg. per 100 ml. with normal phosphorus and phosphatase. X-ray films revealed normal long bones but calcification was seen in the soft tissues around the upper humerus and along both femurs. Her liver gradually enlarged. She continued to deteriorate, grew progressively weaker and died March 30, 1952.

Necropsy. Postmortem examination revealed a thin woman with little subcutaneous fat. The skin was thickened and adherent over the chest, abdomen and lower extremities. No tumors were found in the breast. The liver was enlarged, dark brown in color and contained many metastases varying from 0.5 mm. to 3.5 cm. in diameter. The masses on the surface
of the liver were umbilicated and some of the larger tumor masses had central necrosis with hemorrhage. The stomach was much dilated with a large amount of coffee ground material. The small bowel was red to black in color. At the junction of the jejunum and ileum a small mass in the wall of the bowel produced a right angle kink with obstruction. At this point there was gangrene with peritonitis involving the small bowel and cecum.

The heart was of normal size. On section the tricuspid and mitral valves were much thickened. The tendinous cords were thickened and sclerotic. The pulmonic and aortic valves had great thickening and contraction of the valve flaps. There was no obvious arteriosclerosis.

The microscopic study revealed a malignant tumor of the ileum characterized by nests or columns of cells surrounded by stroma of connective tissue. The cells were fairly regular in outline and had a distinct nucleus without nucleolus. Some cells formed a definite acinar pattern (fig. 2). The pathologic diagnosis was carcinoid of the ileum metastasizing to the liver.

The skin showed much sclerosis together with atrophy (fig. 3). Some of the abdominal skin showed areas of generalized telangiectasia without scleroderma.

In spite of the marked sclerosis of the cardiac valves there was no lesion of rheumatic heart disease.

Patient 2. M. E., a 43-year-old business man, first came to consult one of us (H. B. W.) on April 7, 1950, complaining of flushing attacks and something the matter with his heart. Some years previously he had been told that he had a heart murmur but he had no cardiac symptoms until three weeks before the first visit. Flushing spells began two months after an appendectomy, nine months before he was first seen. He had consulted several doctors and visited different clinics where he was told that he had congenital heart disease or rheumatic heart disease. Three weeks before his visit he noticed that he was gaining weight and was having exertional dyspnea but no orthopnea or paroxysmal nocturnal dyspnea. A week later ankle edema first appeared. It diminished with the employment of a low salt diet and digitalis. Most of the flushing attacks were very mild and transient, just flushing and subjective warmth of the face; but four attacks were very severe and had lasted a long time. In those attacks he also had flushing of the hands and swells of the eyelids and lips. After the flush and the heat left, pallor might occur. The swelling receded slowly. At times there was palpitation with the flushing but usually there was not. There was no pain, lacrimation, rhinorrhea, shortness of breath, hunger, headache or sweating. With the severe attacks there was some apprehension and dizziness. There was no premonitory warning. He knew of nothing he did to bring on the attacks or to stop them.

Initial physical examination revealed a well developed, fairly well nourished white man who was not acutely ill or in discomfort. He weighed

![Figure 3](http://circ.ahajournals.org/)

**Fig. 3.** Lesion of skin with dilated thin walled vessels and sclerotic changes. The papillae are flattened.
167 pounds. Very prominent venous pulsation was seen at the base of the neck bilaterally. There were three visible pulsations and two thumps were palpable, one systolic and one presystolic. The heart was not enlarged. The first tone was replaced by rough systolic murmur. It was maximal in the fourth left intercostal space and well transmitted to the right sternal border and upward into the neck. It was not so loud over the pulmonic area or at the apex but was heard in the axilla. Two diastolic murmurs were heard over the lower right half of the precordium, giving a quadruple rhythm. No diastolic murmur was heard at the apex. The rhythm was regular. The rate was 82, the blood pressure 120/80. The liver was felt 4 cm. below the edge of the ribs. It was soft but not tender. Fluoroscopic examination showed a normal left border. The right border was a little prominent. In the right anterior oblique position, there was no conus fullness. The retrocardiac space was clear. There was no displacement of the barium filled esophagus. An electrocardiogram showed the typical pattern of incomplete right bundle branch block.

The urine was negative. The Wassermann and Kline reactions were negative. Complete blood studies were normal except for the sedimentation rate which was 15 mm. in 1 hour (Cutler). Vital capacity was 3.5 liters.

On subsequent visits the venous pulsations in the neck were clearly identified as presystolic in time. The systolic murmur was audible over a wide area. The diastolic murmur was still heard over the right half of the precordium. He had several more flushing attacks. During a vacation he did not remain on a strict diet and developed some edema. At a subsequent examination repeated transitory flushing was observed. It was brief and resembled a severe flush of embarrassment, though more extensive, affecting the entire face and the bald area of the scalp. Two months after the initial examination he had lost 18 pounds, looked and felt extremely ill and was undergoing continuous flushing during the entire examination. The liver was larger and was moderately tender. The urine now contained albumin and casts. He was again seen by several doctors and in other clinics, finally admitted to another hospital where a preoperative diagnosis of pericarditis was made. At operation the heart was found to be normal. His death occurred 14 months after he was first seen and approximately two years after his first symptom.

The autopsy findings included: malignant carcinoid of the ileum with metastases to the liver, lymph nodes and posterior parietal peritoneum and valvulitis involving all the cardiac valves but most marked in the pulmonic and tricuspid valves.

**Discussion**

Since the syndrome under discussion has been reviewed recently we will not cite the collected cases. Parkes Weber has dealt with the syndrome, though he did not give details of a case he mentioned. Most recent authors have overlooked the observations of Steiner and Voerner recorded in 1909 under the title of Miliary Angiomatosis. They described a 27-year-old man with generalized miliary telangiectases over his whole body. He had severe flushing of the face, body and trunk. A biopsy of the skin showed telangiectasia, formation of new vessels and thrombosis of the larger dilated vessels. The man was under observation for five months. There were no later reports.

We can see no real resemblance of the clinical features of this syndrome to the crisis of pheochromocytoma, the vasomotor storm of thyrotoxicosis, the mottled flush of the diencephalic hypertensive or diencephalic epilepsy, the unilateral flush-sweat of Madame Frey's syndrome or the unilateral burst of flushing seen in very young infants.

The production of serotonin by carcinoid tumors has been demonstrated recently by Lemberg. The possible mechanism by which a potent vasodilating substance, manufactured in the liver, thrown suddenly in potent concentration into the right side of the heart, might damage directly the mural endocardium and the tricuspid and pulmonary valves, is speculative. The clinical features of waves of vasodilatation suggest irregular intermittency and varying concentrations of the agent which must traverse at least the pulmonary capillaries, and perhaps those of the liver.

The brilliant studies of Woolley on biological and molecular antagonists against serotonin suggest that an antagonist might, by neutralizing or blocking its effect, relieve symptoms. It is less likely, but possible, that as an antagonist against the product of a tumor it might inhibit its growth.

Patients with the carcinoid-cardiac syndrome, though not common, present us with a chance to explore new physiologic terrain with equipment already at hand. If for no other reason this justifies our report of these two unusual patients.

**Conclusion**

We have reported two patients with typical clinical features of 1) patterned irregular...
flushing which comes and goes abruptly, 2) mottled cyanosis, 3) diarrhea, 4) asthma, 5) signs of valvular lesions of the right side of the heart and 6) edema and congestive failure. The pathologic findings are 7) carcinoid of the small intestine with metastases to the liver, 8) unusual lesions of the tricuspid and pulmonic valves and 9) telangiectasia with a proliferative and thrombotic disorganization of blood vessels of the skin.

We subscribe to the suggestion of others that this unlikely combination of symptoms and lesions is best explained on a humoral basis; that the carcinoid manufactures serotonin, and releases it into the inferior vena cava erratically; that this in some way produces a morphologic turmoil in valves and endocardium of the right side of the heart, and the torment of brisk and sometimes ephemeral flushing.

We suggest that a molecular antagonist to serotonin should be tested as a possible agent of palliation or cure.

**CONCLUSION IN INTERLINGUA**

Nos presente le sequente "improbabile" combination de symptomas e lesiones:

Clinicamente le sequente se distingueva per 1) rubor a contorno irregular e apparitione e disparitione abrupte, 2) cyanosis marmorata, 3) diarrhea, 4) asthma, 5) signos de lesiones valvular del latere dextere del corde e 6) edema e dysfunctionamento congestive. Le constataziones pathologic esseva 7) tumor carcinoide del intestino tenue con metastases del hepate, 8) lesiones inusuales del valvulas tricuspide e pulmonic, e 9) telangiectasia con disorganizzazione proliferative e thrombotic del vasos sanguinei del pelle.

Nos nos trova de accordo con le opinion de alte autor. que un tal syndrome se explica le melio super un base humoral, i.e. que in illo le tumor carcinoide produce serotonin e disbucca lo erraticamente a in le vena cave inferior e que assi il aden in alicun maniera un disordine morphologic del valvulas e del endocardio al latere dextere del corde e postea le tormento del vive e a vices ephemere rubor.

Nos opina que le cerca de un possibile agente palliative o curative debeca concentrar se super le essaggio de antagonistas molecular de serotonin.

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WILLIAM B. BEAN, DAVID OLCH and HARRY B. WEINBERG

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