Effects of Serotonin Antagonists in Normal Subjects and Patients with Carcinoid Tumors

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The pathogenesis of flushing attacks in patients with malignant carcinoid tumors is attributed to the direct pharmacologic effect of excessive amounts of circulating serotonin. It was hoped that potent serotonin antagonists might relieve symptoms of the carcinoid syndrome in the inoperable patient. The nature of flushing attacks was studied in carcinoid patients and the influence thereon of 3 serotonin antagonists, a benzyl analog of serotonin, bromo-lysergic acid diethylamide, and chlorpromazine. The systemic, subjective, and vascular effects of these antagonists in normal subjects were also investigated.

After the isolation, determination of structure,1-6 and synthesis,7 of serotonin (5-hydroxytryptamine), Erspermer and Asero7 found that the substance producing the fluorescence and staining properties of the chromaffin cells of the intestinal tract was identical with serotonin. Serotonin is formed by enzymatic hydroxylation and decarboxylation of the amino acid, tryptophan, and is degraded in part to 5-hydroxyindoleacetic acid, which is excreted into the urine.8

Malignant gastrointestinal carcinoid tumors, which are believed to be derived from chromaffin cells, may produce excessive amounts of serotonin.9 When enough functioning tumor tissue is present, usually because of hepatic metastases, a syndrome ensues consisting of diarrhea, right-sided valvular heart disease, cyanosis, and an unusual flushing of the skin.10-13 Increased amounts of serotonin are found in the blood of these patients14 and large amounts of 5-hydroxyindoleacetic acid may appear in the urine,15 indicating that this is an endocrine tumor, as was suspected in 1914 by Masson.16

The pathogenesis of the cutaneous vascular changes has not been established although they have been attributed to the direct pharmacologic effect of excessive amounts of circulating serotonin liberated from the tumor. The endocardial sclerotic lesions have been ascribed to a direct action of serotonin;12 destruction in the lungs of serotonin released from liver metastases might account for the failure to find lesions in the left heart. Since elevation of the pulmonary artery pressure may follow the injection of serotonin into dogs17 or normotensive and hypertensive patients,18 Thorson19 suggested that the profound hemodynamic changes associated with attacks of flushing might place an increased strain on the right heart and could be a basis for the development of valvular lesions.

A serotonin antagonist, 1-benzyl-2,5-dimethyl serotonin hydrochloride, abbreviated BAS, a benzyl analog of serotonin (fig. 1) was synthesized by Woolley and Shaw.20,21 Orally administered in doses of 1 mg. per Kg., it protected dogs from the pressor action of intravenous serotonin.22 Another serotonin antimalbolite, 2-bromo-d-lysergic acid diethylamide, hereinafter called bromo-LSD (coded as BOL 148) (fig. 1), was highly effective in blocking the action of serotonin on isolated uterine and intestinal strips;23,24 inhibition of the effects of serotonin on arterial pressure and renal function was also shown in vivo in the intact anesthetized rat.25 A third substance, chlorpromazine hydrochloride, bears no structural resemblance to serotonin, but it has also been shown to antagonize the effects of serotonin in vitro.26-28 It seemed to us that these potent serotonin antagonists might relieve the symptoms of the carcinoid syndrome.

The present study is based on observations
in 5 normal subjects and in 2 patients with malignant carcinoid tumors of the intestinal tract. Neither of the latter patients had clinical evidence of associated endocardial or valvular heart lesions. Both, however, had frequent attacks of flushing. These enabled us to study (1) the nature of this flushing, (2) the influence thereon of 3 serotonin antagonists, BAS, bromo-LSD, and chlorpromazine, and (3) the effects of these antagonists on the vascular action of endogenous and exogenous serotonin, as well as (4) other systemic and subjective effects of these agents.

**Methods**

The effects of intravenous administration of norepinephrine, sodium nitroprusside, serotonin creatinine sulfate, and tetraethylammonium chloride on the arterial pressure of 1 carcinoid patient (case 1) were directly measured by means of a Statham pressure transducer (P-101D) connected to an inelastic polyethylene catheter inserted into a brachial artery, and the pressure changes inscribed on a Brush recorder. The patient was kept supine and without sedatives.

Cardiac catheterization was performed in 1 carcinoid patient (case 1) by Drs. F. Mason Sones and Jean Mignault of the Division of Medicine. After resting arterial and intracardiac pressures were recorded and blood withdrawn for oxygen and serum serotonin* determinations, an intravenous infusion of bromo-LSD (1.0 mg. per minute) was started and determinations repeated after 10 minutes of infusion.

* These analyses were kindly performed by Dr. Sidney Udenfriend, Laboratory of Chemical Pharmacology, National Heart Institute, National Institutes of Health, Bethesda, Md.

**Case Reports**

Case 1. W. J. C., a 29-year-old man, was hospitalized in the Seattle Veterans Administration Hospital in January 1955, with complaints of chronic diarrhea and paroxysmal attacks of flushing of the skin of approximately 3 years' duration. The results

![Chemical structures of serotonin, 5-hydroxyindoleacetic acid, and antimebolites of serotonin (BAS, LSD, and bromo-LSD).](image)

![Psychological effects of bromo-LSD were studied in normal subjects (cases 5, 6, and 7) during intravenous infusions of bromo-LSD alone or during simultaneous infusions of serotonin.](image)
of extensive studies made at that time were reported elsewhere. At laparotomy on February 5, 1955, a firm inoperable mass was found at the pylorus with extension to regional lymph nodes; the liver was enlarged by multiple nodular metastases. The microscopic diagnosis by liver biopsy was malignant carcinoid, secondary in the liver. A postoperative episode of hallucinations and delirium cleared spontaneously after 2 days. Abdominal cramps lessened after discharge, but attacks of flushing continued.

He was referred to us for further study by Dr. D. E. Nolan, Veterans Administration Hospital, Seattle, Washington, on April 15, 1956. Cutaneous changes consisted in persistent cyanosis of the face and paroxysmal attacks of intense purple-red flushing of the face, neck, and extremities. With the latter there were often associated sensations of local heat in the face and generalized tingling of the skin. Palpitation, tachycardia, breathlessness, and sweating were common during the attacks. Episodes of flushing lasted 2 to 3 minutes, occurred spontaneously 10 to 20 times a day, and were often accompanied by abdominal cramps and nausea. Flushes could also be provoked by emotional stress, physical exertion, or evacuation of the bowels, and were aggravated by standing.

The pulse was 80 and the blood pressure 112/72 mm. Hg lying and 100/70 mm. Hg standing. The sclerae were slightly icteric; and optic fundi were normal. The heart was not enlarged, rhythm was regular, and there was a soft murmur at the apex. No clubbing of the digits was seen; peripheral arterial pulsations were normal. The liver was firm, nodular, nontender, and palpable 6 cm. below the costal margin.

Roentgenograms showed the heart to be normal in size and configuration; cardiac pulsation appeared normal during fluoroscopy. An electrocardiogram showed sinus rhythm, slight elevation of the S-T segment in leads I, II, aVL, V4, and slight depression in Lead aVR.

Hemoglobin was 16 Gm. per cent; hematocrit, 58 ml.; red blood count, 6.48 million per mm. with occasional target cells; white blood count, 8,800 per mm., the differential count was normal. The platelet count, bleeding time, coagulation time, clot retraction, prothrombin time, sedimentation rate, icterus index, thymol turbidity, fasting blood sugar, blood urea, and plasma creatinine were normal. The electrophoretic pattern of the serum proteins and the ultracentrifuge lipoprotein pattern were also normal.

The total blood histamine was 11 µg. per cent, which is only slightly higher than usual values (4 to 7 µg. per cent). The urine histamine was 27 µg. and the urine histidine 120 mg. per 24 hours; both values were considered to be within normal limits.

The daily urinary excretion of 5-hydroxyindoleacetic acid averaged 239 mg. per 24 hours and ranged from 174 to 292 mg. per 24 hours (normal range, 2 to 9 mg. per 24 hours).

Case 2. Repeated attacks of vomiting with abdominal cramps and distention began in 1951 in L. C. B., a 61-year-old woman. Three months later, laparotomy revealed a small malignant carcinoid tumor partially obstructing the jejunum; the tumor had invaded the peritoneum and pelvic organs and could not be removed. Clinical improvement followed an enteroenteroanastomosis, but attacks of partial bowel obstruction recurred every 3 to 4 months. In 1955 she became aware of mild to intense red flushing of her face and upper chest 1 to 10 times daily, occurring spontaneously but aggravated by eating or by emotion. Palpitations, headache, and tachycardia accompanied the attacks. Arterial pressure was 130/80 mm. Hg; physical and laboratory examinations gave no evidence for any cardiac lesion. The daily urinary excretion of 5-hydroxyindoleacetic acid averaged 25 mg. per 24 hours (range 14 to 44 mg. per 24 hours).

RESULTS

Studies on Flushing Phenomenon

Histamine phosphate (0.025 mg.) administered intravenously, acetyl-β-methylcholine chloride (15 mg.) or epinephrine (0.25 mg.) given by subcutaneous injection, or alcohol (60 ml.) by mouth did not provoke a typical flush in either carcinoid patient. Atropine sulfate (1.2 mg.) or tetraethylammonium chloride (TEAC) (10 mg. per Kg.) administered intravenously did not prevent spontaneous flushing attacks.

In case 1, in contrast with the effect of epinephrine, the intravenous injection of 10 µg. of norepinephrine produced an intense flush, identical with that of spontaneous attacks; the flush appeared during the depressor phase of 10 to 20 mm. Hg that followed the initial abrupt rise in pressure (fig. 3). Repetitive injection of norepinephrine induced generalized flushing that subsided usually before the blood pressure returned from its depressed to control levels. In the same patient, lowering the blood pressure from 110/72 to 90/60 mm. Hg by intravenous infusion of sodium nitroprusside (100 µg. per ml.) also induced a typical flush; a further decrease of arterial pressure to 80/50 mm. Hg intensified the flush. Intravenous injection of 3
mg. of serotonin creatinine sulfate was followed by a marked pressor response and an intense flush. Repeated doses of TEAC were then injected intravenously for a total dosage of 10 mg. per Kg.; after each injection a mild flush appeared with every fall in arterial pressure. After TEAC, the pressor response to norepinephrine was slightly enhanced and the pressor response to serotonin reduced, but the flushes induced by these drugs or by nitroprusside were neither prevented nor intensified.

Effect of Serotonin Antagonists

Oral Administration of BAS. BAS was given to case 1 by mouth in gradually increasing doses of 100 to 400 mg. (1.8 to 7.5 mg. per Kg.) for 9 days. The drug had no effect on blood pressure and pulse rate, and the number of flushes was the same. The patient thought, however, that their severity was slightly diminished. The daily urinary excretion of 5-hydroxyindoleacetic acid was not affected.

Oral Administration of Bromo-LSD. Bromo-LSD was given to case 2 by mouth in increasing doses up to 20 mg. daily for 7 days. The patient noted mild nasal congestion and thought that the flushes were less intense, but these did not change in appearance nor in rate of recurrence. The range of daily urine excretion of 5-hydroxyindoleacetic acid was unaltered.

Oral Administration of Chlorpromazine. Chlorpromazine was given to case 2 by mouth in daily doses of 100 mg. for 9 months. The patient meticulously kept a daily record of the number and intensity of flushing attacks for 3 months before and during the taking of the drug. The number of flushes did not decrease, and actually became more frequent; however, the intensity and duration of flushing attacks significantly lessened. This was accompanied by a decrease in the severity of the diarrhea and in the frequency of episodes of vomiting and abdominal pain. There was no significant change in average daily urinary excretion of 5-hydroxyindoleacetic acid.

Effects of Intravenously Administered Bromo-LSD

Psychic Effects. In man small doses of bromo-LSD are said to produce none of the bizarre psychic effects noted with lysergic acid diethylamide\(^{23, 31}\) but this is not the case when bromo-LSD is administered intravenously in large doses. Thus, when constant intravenous infusions of bromo-LSD were given to 2 normal subjects (cases 5 and 6) both experienced psychic changes, which became more severe as the infusion continued and persisted for 3 to 4 hours after the infusion was stopped. No hallucinations were noted but there were feelings initially of drowsiness, depression, anxiety and apprehension, followed by feelings of irritation, restlessness, and tenseness, and later, intensely disagreeable sensations of unreality and depersonalization, inexplicable feelings of strangeness and mild confusion. On a subsequent day, both these subjects and another normal subject (case 7) received constant intravenous infusions of serotonin, followed in 10 to 44 minutes by a simultaneous infusion of bromo-LSD. Psychic changes were also experienced during the simultaneous infusions of serotonin and bromo-LSD, although the mental disturbances seemed somewhat less intense than when bromo-LSD was given alone. Furthermore, all other subjects (cases 1–4) have noted similar psychic changes during and after infusion of bromo-LSD; these changes were not modified by single injections of 2 to 4 mg. of serotonin.

Effect on Cardiac Functions. The data obtained during cardiac catheterization in case 1 are summarized in table 1. Pressure tracings indicated no significant valvular lesions. The
difference in oxygen concentration in the pulmonary artery and the right ventricle was not indicative of left-to-right shunt. There was no elevation of pulmonary artery pressure. The resting control systemic resistance of 727 dynes was low compared to a normal mean of about 1250 dynes.

An intravenous infusion of bromo-LSD (1 mg. per minute) was started and determinations were repeated after 10 minutes of infusion. Bromo-LSD had no effect on pulmonary artery pressures. The systemic mean pressure was unchanged. Cardiac output fell slightly from 8.8 to 7.9 L. per minute. The systemic and the total pulmonary resistance changed little during the infusion.

There was no significant difference between serum serotonin levels in hepatic venous blood, mixed venous blood, and peripheral arterial blood, and no appreciable changes in these concentrations during the infusion of bromo-LSD.

**Influence on Vascular Action of Norepinephrine** (table 2). Injections of norepinephrine prior to infusion of bromo-LSD were followed in all subjects, both carcinoid (cases 1 and 2) and normal (cases 3, 4, and 5), by swift rises of arterial pressure of from 20 to 56 mm. Hg systolic and 3 to 32 mm. Hg diastolic. In both carcinoid patients norepinephrine provoked flushing of the face and neck, which appeared as the pressure fell to or below the control level. Arterial pressure did not change appreciably during the intravenous infusion of bromo-LSD nor did the pressor responses to norepinephrine; flushing of the skin occurred in case 1 but not in case 2.

**Influence on Vascular Action of Serotonin** (table 3). Prior to the infusion of bromo-LSD, single intravenous injections of serotonin in both control and carcinoid subjects were followed by flushes of the skin similar to spontaneous attacks occurring in the carcinoid patient and by pressor responses of 29 to 58 mm. Hg systolic and 9 to 57 mm. Hg diastolic (table 3). The flush, involving the face, neck, and extremities, was intense in 4 patients and mild in 1 (case 5). Subjective discomfort was profound in all subjects and characterized by nausea,
paresthesias, breathlessness, and an urge to empty the bowel and bladder. These effects were transient and lasted for about the same length of time, 2 to 3 minutes, as the rise in arterial pressure.

Single injections of serotonin during the infusion of bromo-LSD failed to provoke flushing in cases 2 and 3, the flush was less intense and diffuse in cases 1 and 4, but actually seemed more marked in 1 control subject (case 5). The pressor response in all subjects was similar to that observed when serotonin had been injected alone. The other effects of serotonin were usually milder and less uncomfortable for most subjects, but 1 control subject (case 5) found that the subjective discomfort due to serotonin was intensified during the infusion of bromo-LSD.

**DISCUSSION**

Demonstration of large quantities of serotonin in carcinoid tumor extracts,9 hyperserotoninemia,13, 14 and increased urinary excretion of serotonin end-products15 in carcinoid patients, all implicate serotonin in the pathogenesis of the vasomotor episodes. This assumption is supported by precipitation of flushes in some patients by palpation of the tumor.13, 32, 33 Flushing was said not to occur as a result of intravenous injections of serotonin in man;34-36 intravenous infusions of 0.8 to 1.2 mg. per minute of serotonin creatinine sulfate produced tingling and burning of the face but no flush was seen.15 However, in the present study, rapid single intravenous injections of larger (1.8 to 4.0 mg.) doses of serotonin provoked mild to moderate, at times intense, flushes in normal as well as carcinoid subjects. This was also observed in hypertensive patients.37 The flushes appeared to be similar in every way to the paroxysmal attacks in carcinoid patients.

Hypotension and syncope accompanied by flushing was observed in several carcinoid patients.13, 32, 36 One of our carcinoid patients (case 1) had, at rest, a low systemic resistance, and lowering of his arterial pressure by several different agents was invariably followed by attacks of flushing. This suggests that hypotension either directly or by vasomotor reflexes stimulates the tumor to release increased amounts of serotonin into the blood. Either assumption presupposes that the tumor is innervated.

The intermittent character of flushing attacks in the carcinoid syndrome is most likely associated with variations in the output of serotonin by the tumor; another possibility might be episodic changes in the proportion of free, biologically active serotonin to platelet-bound serotonin circulating in the peripheral blood. It is unlikely that a generalized parasympathetic discharge is involved, since flushing was not prevented by atropine or tetraethylammonium chloride.

An oral dose of BAS of 400 mg. a day failed to relieve symptoms or produce sedation in case 1. This lack of sedative effect contrasts with that reported39 in hypertensive patients given much smaller amounts (160 mg. per day). Bromo-LSD administered by mouth in doses up to 20
mg. daily also failed to relieve flush and diarrhea in case 2; smaller oral doses of bromo-LSD (1 to 15 mg. a day) did not antagonize the circulatory effects of serotonin in other carcinoid subjects. The dosages of these antimetabolites may be inadequate but they were larger than those used before and increased doses did not seem practicable.

Intravenous infusion of bromo-LSD in large doses (0.5 to 5.0 mg. per minute) did not effectively block the pressor response to serotonin. Serotonin-induced flush and other pharmacologic effects of serotonin were diminished or failed to appear in some subjects during infusion of bromo-LSD but this was not a consistent observation; in 1 normal subject (case 5) there was an aggravation of all reactions to serotonin. In normal rats, bromo-LSD (2.5 Gm. per Kg. intravenously) inhibited the effects of subsequent injections of serotonin on arterial pressure and renal function, but had little effect when given during serotonin infusion, an observation consistent with the failure of this agent to influence the course of the carcinoid syndrome.

Chlorpromazine was reported to alleviate the diarrhea of a patient with malignant carcinoid. In our experience, administration of chlorpromazine to a carcinoid patient (case 2) decreased the intensity of flushing attacks and the severity of abdominal symptoms, but had no effect on 5-hydroxyindoleacetic acid excretion.

Lysergic acid diethylamide, a potent serotonin antagonist induces in man temporary mental aberrations accompanied by hallucinations. It was postulated by Woolley and Shaw that these psychic effects might arise by inhibition of the action of serotonin in the central nervous system. This hypothesis was questioned by Cerletti and Rothlin, since 2-bromo-d-lysergic acid diethylamide in doses of 1 to 2 mg. (20 times as great as lysergic acid) did not produce psychic disturbances in man even though it was a potent serotonin antagonist in vitro. We have found that large doses (a total of 15 to 160 mg.) of bromo-LSD, given by constant intravenous infusion, provoked definite psychological changes in all normal subjects who received the drug, as well as in 2 carcinoid patients. The intensity of the subjective response to the drug appeared to be dependent, in part, on the cultural background and ability for self-observation of the subject, and, in part, to the total amount of drug received. The mental changes did not include hallucinations but were similar in most other respects to those induced by LSD.

The relatively weak central nervous effects of bromo-LSD, as compared to LSD, could be due to more rapid metabolism and excretion from the body, to lesser ability to penetrate brain tissue or to less powerful binding by receptor sites. Serotonin does not appear to penetrate the blood-brain barrier to any appreciable extent. Thus, although the psychic effects of bromo-LSD, like those of LSD, might be due to serotonin antagonism, it was to be expected that such mental disturbances were not prevented by the hyperserotonemia present in carcinoid patients, nor effectively antagonized by intravenous infusions of serotonin in normal subjects.

Conclusions

Intravenously administered serotonin in man in sufficient dosage caused flushing and reproduced other clinical manifestations of the carcinoid syndrome. Lowering of the arterial pressure in 1 carcinoid patient invariably provoked attacks of flushing, suggesting that hypotension directly or through vasomotor reflexes may stimulate the tumor to liberate excessive amounts of serotonin.

1-Benzyl-2,5 dimethyl serotonin (BAS) and 2-bromo-d-lysergic acid diethylamide (bromo-LSD), though potent serotonin antagonists in vitro, were ineffective in controlling symptoms in carcinoid patients when given by mouth. Chlorpromazine appeared to be partially effective in alleviating the symptoms of the carcinoid syndrome and may be of value in the symptomatic relief of the carcinoid syndrome.

Bromo-LSD, when intravenously administered, did not effectively block, although it may have diminished, the vascular and other pharmacologic effects of intravenously injected serotonin. Bromo-LSD did not cause hallucinations, but in large intravenous doses produced psychic disturbances that otherwise
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resemble those regularly observed after small doses of lysergic acid diethylamide. These psychic effects of bromo-LSD might be due to inhibition of some central nervous action of serotonin but they were not prevented by the hyperserotonemia present in carcinoid patients and were not alleviated by infusions of serotonin in normal subjects, as was to be expected by the failure of serotonin to pass the blood-brain barrier.

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SUMMARIO IN INTERLINGUA

Le administration intravenose de serotoninna in homines—in doses sufficiente—causava enchymoste e reproduceva altere manifesta- tiones clinic del syndrome carcinoide. In un caso, le reduction del pression arterial in le presentia del syndrome carcinoide resultava invariablemente in attaccos de enchymoste. Isto pare indicar que hypotension es capace—directemente o via reflexos vasomotori—a stimular le tumor a liberar excessive quantitates de serotonin.

1-Benzyl-2,5-dimethyl-serotonina (BAS) e 2-bromo-d-(acido lysergic)-diethylamido (bromo-LSD)—ben que ambes es potente antagonistas a serotoninna in vitro—nonsucce- deva, post administrationes oral, a subjugar le symptomas in patientes carcinoide. Chlor-promazina pareva esser partialmente efficace in alleviar le symptomata del syndrome carcinoide e va possibilemente esser de valor in le alleviamento symptomatic del syndrome carcinoide.

Bromo-LSD in administration intravenose non blocava efficacemente (ben que illo possibilemente reduceva) le effectos vascular e alteremente pharmacologique de serotoninna in injectiones intravenose. Bromo-LSD non causava hallucinationes, sed post le administration de grande doses intravenose illo produceva distributiones psychic que resimilava le effectos regularmente observata post parve doses de diethylamido de acido lysergic. Il es possible que este effectos psychic de bromo-LSD resulta del inhibition del un o del altre action de serotoninna in le systema nervose central, sed illos non eseva prevenite per le hyperserotoninemia que es presente in patientes carcinoide, e illos non eseva alleviate per infusiones de serotoninna in subjectos normal, como on haberea expectate Io, viste le facto que serotoninna non transpassa le bariera sanguino-cerebral.

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**Medical Eponyms**

By Robert W. Buck, M.D.

**D’Espine’s Sign.** In an article entitled “The Sea Cure of Serofula at the Dollfus Asylum of Cannes” (La cure marine de la serofula à l’asile Dollfus de Cannes) in the Bulletin de l’académie 52: 400-420 (November 8) 1904, Adolphe D’Espine (1846-1930) says:

“The first signs of bronchial adenopathy are obtained by auscultating the voice and are nearly always found in the immediate neighborhood of the vertebral column between the seventh cervical vertebra and the first dorsal vertebra, either in the sub-spinous fossa or lower in the interscapular space. These signs consist in a super-added timbre in the voice which one may call a whisper in the first stage and bronchophony in a more advanced stage.”

A more complete description of the sign occurs in the article “Early Diagnosis of Tuberculous Bronchial Glands in Children” (Le diagnostic précoce de la tuberculose des ganglions bronchiques chez les enfants) in the Bulletin de l’Académie de Médecine 57: 167 (January 29) 1907, as follows:

“We have the patient pronounce as clearly as possible trois cent trente-trois. In the case of infants, we must be content with auscultation while the child is crying. We first listen over the cervical vertebrae with a small-mouthed stethoscope. . . We then distinctly perceive, as Laennec pointed out, the characteristic tracheal murmur. . . . In the normal infant this tone stops suddenly at the level of the spinous process of the seventh cervical vertebra where the lung begins.

“In bronchial adenopathy, on the other hand, the bronchial tone is heard over a variable area extending between the seventh cervical and the fourth and fifth dorsal vertebrae. . . .

“When auscultation of the spoken voice or of the cry fails to give any result, we ask the child, if he is old enough to understand, to speak in a whisper, when, if there is adenopathy, an acoustic phenomenon is heard analogous to Bacelli’s aphonic pectoriloquy. . . .”

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