

# ACTION OF PROMETHAZINE ON SYSTEMIC BLOOD PRESSURE, PULMONARY ARTERY PRESSURE, AND PULMONARY BLOOD-FLOW

BY

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Since the report of Winter (1948) that some antihistamine drugs potentiate the hypnotic effect of barbiturates in animals, the former have been used with increasing frequency by anaesthetists (Beard, 1954). Promethazine hydrochloride ("phenegan") has been administered alone or in association with a barbiturate or pethidine as a sedative before cardiac catheterization, and it therefore seemed necessary to determine the effects of the drug on the circulation. This paper reports the results of the investigation.

### Material and Methods

Six cases undergoing cardiac catheterization for diagnostic purposes were investigated: three had mitral stenosis, in two an atrial septal defect was confirmed, and in one with a dilated aorta no abnormality was found. Promethazine hydrochloride in doses of 50 or 25 mg. was administered by intravenous injection. The premedication is shown in the Table.

Pulmonary artery and brachial artery pressures were measured continuously throughout the observations using capacitance manometers. Simultaneous samples were taken at intervals from pulmonary and brachial arteries for blood gas analysis. In Case 3 the pressure measurements and blood samples were taken from the outflow tract of the right ventricle. Oxygen consumption was measured by breathing air from a spirometer of "box-bag" type (Donald and Christie, 1949); two observations were made in each case—one during the control period before the injection of promethazine, and one after the last blood samples had been taken. The second estimation was used to calculate the pulmonary blood-flow after administration of the drug. The heart rate was estimated from an electrocardiogram taken simultaneously throughout the observations.

The patients were supine, with one or two pillows under the head. The control period lasted approximately 20 minutes in each case, and the experimental period was continued for from 17 to 22 minutes after injection of the drug.

### Results

The results are shown in the Table. The data obtained after injection of promethazine are presented as average readings over four five-minute periods: from 2 to 7, 7 to 12, 12 to 17, and 17 to 22 minutes after the injection.

No significant change in systemic blood pressure occurred after injection of the drug. Changes in pulmonary artery pressure were small, though a slight rise occurred in Case 5. Changes in oxygen consumption were small over the short period of the observations, values tending to increase in four cases, decrease in one, and remain unchanged in one. In the three cases with mitral stenosis and the patient with the dilated aorta, changes in arteriovenous oxygen difference were slight and the calculated cardiac output showed little change. In the two cases with atrial septal defect the arteriovenous oxygen difference decreased strikingly in one case, but showed a small increase in the other. Calculated pulmonary blood-flow therefore increased considerably in the former and decreased slightly in the latter. The heart rate increased slightly or moderately in all six cases.

An excellent hypnotic effect was obtained in Cases 1 to 4. Cases 1, 3, and 4 were already quiescent from soluble sodium amylobarbitone, but promethazine injection resulted in greatly increased sedation. In Case 2 adequate sedation was obtained from promethazine alone. Cases 5 and 6 were becoming restless before the administration of promethazine; after the injection some increase in sedation occurred, but this was accompanied by disorientation and inability to co-operate.

### Discussion

For the purposes of the investigation of circulatory function or the premedication of cases with considerable cardiac disability, it is an advantage to use a sedative which produces the necessary hypnotic effect without appreciably altering the circulatory state. Promethazine hydrochloride has been shown to produce little effect on the circulation, apart from a mild tachycardia, in six cases undergoing cardiac catheterization. In addition, promethazine has been shown in animals to have a quinidine-like action in lengthening the refractory period of the auricles (Hutcheon, 1953), and may therefore be of value in the prevention of cardiac arrhythmias. It appears, however, that some sedative in addition to promethazine may be necessary in the restless or apprehensive subject.

Case No.	Diagnosis	Age, Sex	Premedication	Dose of Promethazine (mg. i.v.)	Pulmonary Artery } Pressure (mm. Hg)					Arteriovenous O <sub>2</sub> Diff. (ml./l.)					Oxygen Consumption (ml./min.)		Heart Rate				
					Brachial Artery } Pressure (mm. Hg)					Pulmonary Blood-flow (l./min.)											
					Control	2-7'	7-12'	12-17'	17-22'	Con.	2-7'	7-12'	12-17'	17-22'	Bef.	Aft.	Con.	2-7'	7-17'	12-17'	17-22'
1	Dilated aorta, S.R.	27 M	Sod. amylobarbitone 3 gr. per os	25	19/6 120/76	19/6 117/76	21/7 113/78	19/6 110/76	—	40 6.3	37 7.5	37 7.5	38 7.3	—	250	276	80	94	92	93	—
2	A.S.D., S.R.	15 F	None	25	15/7 125/80	14/6 120/83	16/8 120/83	16/8 122/82	14/6	17 15.1	17 14.8	18 14.0	18 14.0	21 12.0	257	252	94	105	106	110	106
3	M.S., S.R.	20 F	Sod. amylobarbitone 3 gr. p.o.	50	34/1* 125/64	33/1* 129/68	34/2* 128/64	35/2* 136/68	—	40 5.7	46 6.0	52 5.3	48 5.8	—	229	276	71	90	92	102	—
4	A.S.D., S.R.	18 M	Sod. amylobarbitone 3 gr., pronestyl 1 g. p.o.	50	18/7 107/65	18/7 105/65	17/6 109/64	18/6 112/63	18/7 109/65	28 9.0	30 8.1	34 7.1	—	20 12.1	252	242	92	112	110	110	110
5	M.S., A.I., S.R.	44 M	Sod. amylobarbitone 3 gr. p.o.	50	28/11 103/67	33/16 110/67	39/19 111/68	38/18 111/69	36/17 112/69	46 6.0	—	49 6.2	—	55 5.5	278	302	66	68	73	74	76
6	M.S., A.F.	47 F	Sod. amylobarbitone 3 gr. p.o.	50	50/24 166/98	53/25 166/98	53/25 167/98	52/25 170/98	52/25 170/100	60 3.6	—	—	64 4.0	60 4.2	213	253	80	80	88	86	88

\* Right ventricular pressures. A.S.D. = Atrial septal defect. A.F. = Auricular fibrillation. A.I. = Aortic incompetence. M.S. = Mitral stenosis. S.R. = Sinus rhythm.

**Summary**

The effects of intravenous injection of 25–50 mg. of promethazine hydrochloride have been studied in six cases undergoing cardiac catheterization. No significant changes occurred in the systemic blood pressure. One case showed a slight rise in pulmonary artery pressure. Pulmonary blood-flow showed little change in four cases, an increase in one, and a slight decrease in one. The heart rate increased in all cases.

The small circulatory changes associated with a satisfactory hypnotic effect suggest that promethazine is a suitable drug for the premedication of cardiac cases.

We are indebted to the technical staff of the Institute of Cardiology for assistance in making these observations.

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## CARCINOMA OF THE BRONCHUS WITH BENCE JONES PROTEINURIA

BY

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Since the first description by Henry Bence Jones (1848) of the substance which now bears his name, interest has continued in the nature of Bence Jones protein. Its association with conditions other than multiple myelomatosis has only rarely been reported. Geschickter and Copeland (1928), from their own experience and a review of the literature, collected 26 cases of Bence Jones proteinuria in diseases other than multiple myelomatosis. Nine of these cases had skeletal metastatic tumours. Copeland (1931) reported three cases of carcinoma of the breast with skeletal metastases in which Bence Jones proteinuria was demonstrated. There have been few reports in recent literature, and Snapper (1949), from his own experience, believed Bence Jones proteinuria to be almost pathognomonic of multiple myelomatosis.

The two cases reported here are cases of carcinoma of the bronchus, confirmed at necropsy, in which Bence Jones proteinuria was demonstrated. An additional interesting feature was the sternal marrow of the first of these cases, which showed a "myeloma-like" picture.

**Case 1**

A man aged 74 had been for some time in poor health, complaining of anorexia and general malaise. Two months before admission to hospital he had noticed an exacerbation of his chronic cough with the production of a moderate amount of purulent sputum. Two weeks before admission his condition had deteriorated and he had developed feverishness and a sore throat. There was no relevant family or previous medical history. On October 6, 1952, he was admitted to Crumpsall Hospital, Manchester, under Dr. M. D. Milne. Examination revealed an emaciated ill man, sweating slightly. His temperature was 100.2° F. (37.8° C.), pulse 112 and regular, and B.P. 120/65. His heart was normal. There were diminution in expansion, dullness to percussion, and diminished air entry over the right lower lobe. The oral mucosa was inflamed. There was no hepatomegaly or splenomegaly and no lymphadenopathy.

*Investigations.*—Urine : S.G., 1012 ; Fehling's, Benedict's, and Rothera's tests were negative. Testing for albumin revealed a moderate amount of Bence Jones protein. The methods for detection of Bence Jones proteinuria outlined by Jacobson and Milner (1944) were used both in this and in the following case. X-ray examination of the chest showed right-lung collapse together with a large cavity with a fluid level, the appearances being those of a breaking-down neoplasm. Antero-posterior and lateral views of the skull showed no abnormality. Blood : Hb, 8.5 g. ; white cells, 13,300 (polymorphs 84%, lymphocytes 10%, monocytes 6%). The sputum was negative for tubercle bacilli. Serum urea was 54 mg. per 100 ml., serum protein 5.5 g. per 100 ml. (albumin 2.8 g., globulin 2.7 g.), serum calcium 7.5 mg. per 100 ml., serum inorganic phosphate 2.6 mg. per 100 ml.

*Sternal Marrow.*—The marrow smear showed an average cellularity and a normoblastic erythropoiesis. The striking feature was the preponderance of plasma cells, which formed about 40% of the nucleated cells. Many were atypical, having two and occasionally three nuclei. In addition many reticulum cells were present. The picture was thought to represent the reaction of the marrow to malignant infiltration, though clumps of tumour cells were not demonstrated and sections of marrow fragments gave no diagnostic assistance.

*Clinical Course.*—Treatment with antibiotics failed to alleviate a short downhill course, and the patient died on December 10.

*Necropsy Findings.*—The right lung weighed 2,100 g. A large growth arising from the right main bronchus had extended throughout most of the right lung. Areas of necrosis, dilated bronchi containing pus, and a right-sided empyema were present. Both kidneys and the right adrenal contained tumour secondaries. Microscopy of the primary and secondary tumours showed an anaplastic oat-celled carcinoma.

**Case 2**

A man aged 40 had been for three months in poor health associated with loss of weight and lack of energy. He complained of dyspnoea and a non-productive cough ; there was no haemoptysis. One brother and a sister had died of pulmonary tuberculosis. His previous medical history was not relevant. On March 6, 1953, he was admitted to Crumpsall Hospital, Manchester, under Dr. R. W. Luxton. Examination revealed a pale ill man ; temperature 98° F. (36.7° C.), pulse 88 and regular, B.P. 130/80. His heart was normal. Trachea to right, diminution in expansion, percussion note and air entry over both bases. The liver was enlarged 2 in. (5 cm.) below the costal margin ; the spleen was just palpable ; there was no lymphadenopathy.

*Investigations.*—Urine : S.G., 1020 ; Fehling's, Benedict's, and Rothera's tests were negative. Testing for albumin revealed a moderate cloud on boiling and with sulphosalicylic acid. Subsequent investigation revealed in addition to albumin the presence of a moderate amount of Bence Jones protein. X-ray examination of the chest showed partial consolidation of the right middle lobe, the appearances suggesting a neoplasm. The patient's condition precluded further radiological examination. Blood : Hb, 11.5 g. ; white cells, 11,000 (polymorphs 73%, lymphocytes 12%, eosinophils 3%, basophils 1%, monocytes 6%, myelocytes 5%) ; normoblasts, 3 per 100 white cells. The sputum was negative for tubercle bacilli. Serum proteins, 5.7 g. per 100 ml. (albumin 2.6 g., globulin 3.1 g.) ; serum alkaline phosphatase, 17 King-Armstrong units per 100 ml. Unfortunately, specimens of urine and serum were several weeks old when submitted for electrophoresis and, although kept frozen solid, did not give satisfactory electrophoretic patterns.

*Sternal Marrow.*—The marrow smear showed a depression of erythropoiesis associated with the presence of many undifferentiated cells resembling reticulosarcoma or anaplastic carcinoma. Clumps of tumour cells were not demonstrated, nor did section of marrow fragments give additional information.