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Title: Radiology
 Title Abbrev: Radiology
 Citation: 1951 Sep;57(3):384-94
 Article: Nitrogen mustard as an adjunct to radiation in the
 Author: ROSWIT B;KAPLAN G
 NLM Unique ID: 0401260 Verify: PubMed
 PubMed UI: 14883322
 ISSN: 0033-8419 (Print) 1527-1315 (Electronic)
 Fill from: **Any format**
 Publisher: Radiological Society of North America, Easton, PA :
 Copyright: Copyright Compliance Guidelines
 Authorization: RW
 Need By: N/A
 Maximum Cost: **\$15.00**
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Nitrogen Mustard as an Adjunct to Radiation in the Management of Bronchogenic Cancer¹

BERNARD ROSWIT, M.D.,² and GUSTAVE KAPLAN, M.D.³

New York, N. Y.

IT is generally agreed that pulmonary resection offers the patient with bronchogenic carcinoma his best chance for cure. Unfortunately, most cases are inoperable when first seen. Of the 400 patients with bronchogenic carcinoma seen at the Veterans Administration Hospital in the Bronx (N. Y.) in the past four years, 90 per cent came too late for surgery. At the Hines Veterans Hospital, 95.4 per cent of 1,057 such patients admitted from 1937 to 1947 were already beyond any attempt at salvage by surgical resection (1). This distressing picture is reflected in other hospitals and clinics. It may be estimated that in 1949 there were in this country about 28,000 new patients with bronchial cancer, compared to 10,000 in 1939 (34).

Unless treated by irradiation, inoperable bronchogenic carcinoma runs its lethal course rapidly and inexorably, complicated by distressing signs and symptoms, both local and systemic. Of 584 non-irradiated inoperable patients, not one survived more than one year after the onset of the disease, according to the combined reports of Leddy and Moersch (18) at the Mayo Clinic, Widmann (31) at the Pennsylvania General Hospital, and Ariel *et al.* (1) at the Hines Veterans Hospital.

On the other hand, our own experience with the roentgen treatment of 605 inoperable cases in the last fifteen years has demonstrated that, when radiation therapy was feasible, effective relief from intractable local symptoms was often possible. Indeed, prolongation of useful life for many months, and even years, was sometimes

accomplished, particularly when the patient's physical condition was such that cancerocidal doses (5,000 to 6,000 r) could be approached. An occasional rare cure may be achieved. These observations are supported by the experience of others in a group of 508 roentgen-treated cases reported in the literature (6, 18, 28, 31).

It is not possible, however, to give to every inoperable patient the benefits which irradiation can offer. At intervals in the course of the disease irradiation may seem to be ineffective or, for various reasons, even unfeasible. An effective adjunct to radiotherapy would therefore, appear, to be most desirable during these periods. The object of this paper is to present the results of our investigation of nitrogen mustard or HN₂,—methyl-*bis* (beta chloroethyl) amine hydrochloride—employed in this role.⁴

RATIONALE OF NITROGEN MUSTARD TREATMENT

The early investigations of Gilman (11), Goodman (12), Jacobson (13), and Karnofsky (14 and 15), and their co-workers, with nitrogen mustard in human lymphomas, excited our interest in investigating its role as an adjunct to radiotherapy in a variety of malignant disorders. The study was begun in the Radiation Clinic in January 1947, in collaboration with the Committee on Growth of the National Research Council. Bronchogenic carcinomas were included because of scattered reports of clinical benefit by other investigators (33). In an earlier communication (21)

¹ Presented at the Thirty-sixth Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 10-15, 1950. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

² Chief, Department of Radiotherapy, Veterans Administration Hospital, Bronx, New York.

³ Assistant Chief, Department of Radiotherapy, Veterans Administration Hospital, Bronx, New York.

⁴ Nitrogen mustard (mustargen) supplied through courtesy of Merck & Co., Rahway, N. J.

we reported our experience with nitrogen mustard as an adjunct to radiation in a group of 87 patients with a variety of neoplastic diseases, including 16 subjects with inoperable bronchogenic carcinoma. Nine of the 16 cases showed a favorable response to the chemotherapeutic agent.

Nitrogen mustard is a systemic toxin with special selectivity for the blood-forming organs, the gastro-intestinal tract, and actively proliferating tissues. Its physiological action on tissues is remarkably rapid, and its physical half life, or the time required for conversion into the highly reactive imine form, is only 90 seconds. One might therefore expect the lung to be the first organ to receive the full impact of the agent after intravenous injection. The pulmonary tissue is probably the only one exposed to the full dose, although some of the material may already have reacted with constituents of the blood. Recent studies on mice by Seligman, Friedman, and Rutenburg (24) with radioactive HN2 tagged with I^{131} have demonstrated the highest concentration in the lung, blood, lymph nodes, spleen, and kidney. The lung was the only tissue in which radioactivity persisted after injection.

There is a remarkable paucity of histologic findings to explain the clinical changes observed. The minimal changes, however, that have been reported by Spitz (27), Lynch, Ware, and Gaensler (19), and Gaensler *et al.* (10) are similar to those seen after small doses of ionizing radiation. In no instance was the tumor entirely eradicated. Even in small amounts, however, HN2 is highly cytotoxic and nucleotoxic, powerfully inhibiting a variety of cellular enzymes and inhibiting vital metabolic processes such as cellular respiration.

CLINICAL MATERIAL

Since January 1947, 150 patients with inoperable bronchogenic carcinoma have been accepted for treatment in the Radiation Clinic of the Veterans Administration Hospital in the Bronx. Forty of these patients received HN2 as an adjunct to roentgen therapy when radiation was un-

feasible or no longer effective because of (a) radioresistance, (b) severe radiation sickness, (c) exhaustion of skin portals, (d) intractable systemic symptoms, (e) acute mediastinal compression, and (f) far advanced disease with generalized metastases. The 16 cases mentioned in our preliminary communication are included in the present report. With a single exception, the diagnosis of bronchogenic carcinoma was histologically proved. In that instance there was overwhelming clinical, radiological, and bronchoscopic evidence of the disease. The histologic types were as follows: epidermoid carcinoma, 8; anaplastic carcinoma, 23; mucous-gland carcinoma, 4; and unclassified carcinoma, 5. Among the anaplastic tumors were 4 of the "oat-cell" variety.

TECHNIC

Nitrogen mustard was given intravenously in doses of 0.1 mg. per kilogram of body weight, once daily for four consecutive days. This constituted a single course which was repeated, if indicated, but only after an interval of four weeks or longer to permit complete recovery of the bone marrow. No patient was given more than two courses. In no case were roentgen therapy and nitrogen mustard employed simultaneously.

Immediately before treatment, 10 c.c. of sterile normal saline was introduced into a glass vial containing 10 mg. of the crystalline salt, thus creating a solution of 1.0 mg. of HN2 per cubic centimeter of solution. The appropriate dose was at once withdrawn and injected into the vein, or into the rubber tubing of a running infusion of normal saline. The latter technic is probably more satisfactory and minimizes the danger of a chemical phlebitis. Local extravasation of the drug will result in necrosis of tissue.

Gastro-intestinal symptoms such as nausea and vomiting were encountered in the majority of the cases after the first dose, beginning from one to eight hours after injection. These complaints were less common following subsequent injections and

appeared to be modified by the use of hypnotics. The hemopoietic changes, particularly leukopenia and thrombocytopenia were not usually serious, but frequent blood studies are a desirable precaution. Marked bone marrow depression before treatment must be regarded as a contraindication to HN2 therapy. Other toxic reactions, local and systemic, have been reported in detail in earlier communications (21, 23).

RESULTS

A favorable response to nitrogen mustard therapy was observed in 30 of the 40 patients (75 per cent), in the form of a remission period averaging three and a half weeks. In 10 patients the results were poor or negligible. In reaching these conclusions the following criteria were used:

(1) *Subjective Response:* Relief from systemic symptoms such as fever, night sweats, weakness, and anorexia, and from local symptoms such as intractable chest pain, cough, and dyspnea. A favorable *subjective* result was achieved in 30 cases for periods varying from one week to seven weeks. Statistical analyses can hardly reflect the dramatic clinical improvement in some patients, grateful for even a brief respite from insufferable discomfort.

(2) *Objective Response:* Improvement in the signs of superior vena cava compression syndrome (Fig. 4A and B), gain in weight, resorption of pleural fluid, decrease in pulmonary lesions, disappearance of atelectasis, and regression of obstructive pneumonitis. A favorable *objective* result was noted in 19 of the 30 cases with a favorable subjective response. Immediate *radiographic* evidence of improvement, however, was encountered in only 4 instances (Figs. 4C and D, 5A and B, 6A and B). In some instances progression and metastases were noted even in the face of definite clinical improvement (Fig. 1A and B).

(3) *Degree of Rehabilitation:* Improvement of the patient to the point where a course of radiotherapy could be initiated, resumed, or completed; discharge from hospital to home, maximum hospitalization

benefit having been achieved. In 12 of the 30 patients responding favorably, improvement in severe systemic symptoms was of such a degree that definitive x-ray therapy could be initiated. Five patients responded so well that they were discharged to their homes.

Patients with the anaplastic type of lesion showed the highest percentage of favorable response (Table I). The re-

TABLE I: RESPONSE IN RELATION TO HISTOLOGY

Histologic Types	Number of Cases	Result	
		Favorable	Unfavorable
Epidermoid carcinoma	8	4	4
Anaplastic carcinoma	23	20	3
Mucous-gland carcinoma	4	2	2
Unclassified carcinoma	5	5	0

sponse in relation to the six primary indications for adjunct HN2 treatment are shown in Table II.

TABLE II: RESULTS ACCORDING TO INDICATIONS FOR TREATMENT

Indications	No. of Cases	Response to HN2	
		Favorable	Poor
(a) Radioresistance	7	2	5
(b) Severe radiation sickness	2	2	0
(c) Exhaustion of skin portals	1	1	0
(d) Intractable systemic symptoms	15	12	3
(e) Acute mediastinal compression	9	7	2
(f) Very far advanced disease	6	6	0
Totals	40	30	10

(a) There were seven radioresistant subjects who failed to respond to an initial course of radiotherapy and therefore received HN2. Two of these patients reacted very well to the chemotherapeutic agent.

CASE 1. A 63-year-old grocer with a Pancoast tumor experienced the type of unrelenting pain in the left shoulder girdle, radiating to the arm, which is so characteristic of this variety of bronchial carcinoma. In our experience these tumors are generally radioresistant. Although radiation was being rapidly delivered to the lesion and a level of 1,600 r

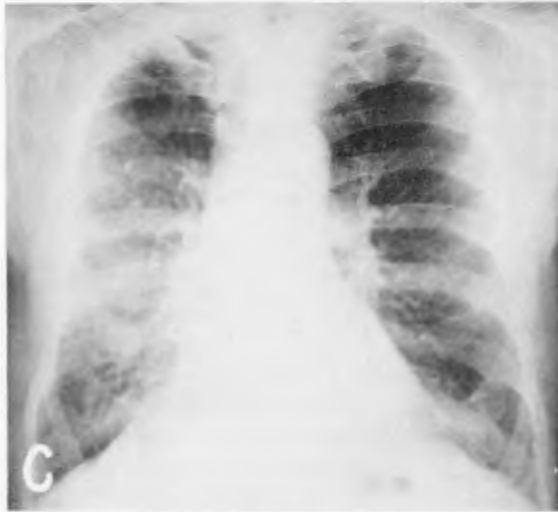


Fig. 1. Case 3. A. Bronchogenic carcinoma, with right mediastinal mass. Radiotherapy started (300 r depth dose). Intractable radiation sickness precluded further radiotherapy. HN2 was administered.

B. After HN2, there was marked subjective improvement, but the roentgenogram reveals progressive disease. One week later, the patient was able to tolerate more radiation.

C. After x-ray therapy (1,500 r depth dose). Marked improvement radiographically and subjectively. The patient was able to go home and remission lasted nearly four months.

had been attained, the pain appeared to be growing steadily more severe. A course of HN2 produced immediate relief.

CASE 2: A 48-year-old auto mechanic was refractory to 4,500 r (depth dose) administered for severe chest pain secondary to pleural invasion by bronchial carcinoma. A single course of HN2 produced striking relief from pain and improvement in appetite and well-being. The patient was able to return home and to resume normal activity for a period of eight weeks.

(b) HN2 was employed in 2 subjects experiencing uncontrollable radiation sickness which interrupted a course of prescribed radiotherapy. Both patients enjoyed a favorable response. Radiation sickness as a complication has become uncommon in our Clinic since the introduc-

tion of desoxycorticosterone acetate (8) for its control.

CASE 3: A 53-year-old bedridden police officer with a large endobronchial tumor and enlarged mediastinal nodes received radiation to the mediastinum for the relief of pain, dyspnea, and obstructive pneumonitis (Fig. 1A). He became nauseated and vomited repeatedly after only 300 r (depth dose) had been delivered. In spite of medication, the radiation illness appeared intractable, and a course of HN2 was administered for management of the neoplasm. Dyspnea improved, fever and night sweats diminished, and the patient became ambulant. Radiotherapy was immediately resumed, because of radiographic evidence of extension of the tumor (Fig. 1B), a total of 1,500 r (depth dose) being delivered to the chest without further difficulty. Clinical and radiographic improvement followed promptly (Fig. 1C). The patient was discharged to his home and remained well for nearly four months.

(c) The exhaustion of available skin portals as a result of marked radiation reactions is occasionally an obstacle to completion of effective radiotherapy. One such case was treated with HN2. Precisional cross-fire radiation through multiple portals (7, 22), rotation therapy, and super-

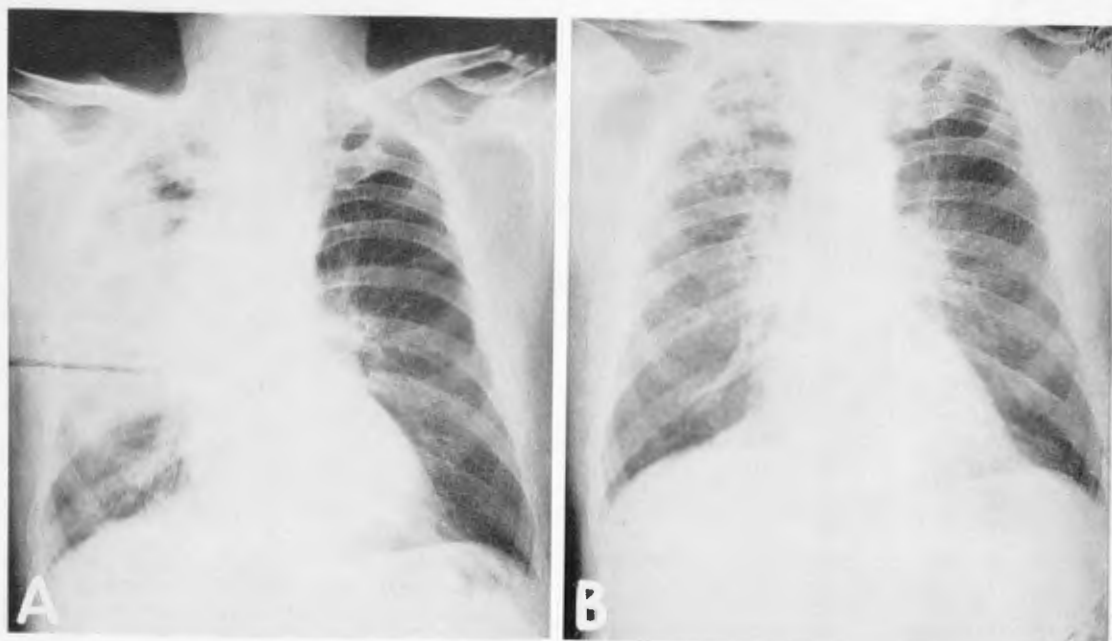


Fig. 2. Case 5. A. Mediastinal nodes and obstructive pneumonitis due to bronchogenic carcinoma, associated with intractable chest pain, cough, and dyspnea.

B. Almost complete disappearance of tumor and obstructive pneumonitis after 6,000 r depth dose. Clinical remission lasted six months. A repeat course of radiation was then made possible only with the aid of nitrogen mustard therapy.

voltage radiation promise to minimize this complication.

CASE 4: A 40-year-old veteran received 2,500 r (depth dose) to the chest for relief of superior vena cava compression syndrome secondary to anaplastic bronchogenic carcinoma. Marked improvement was achieved, and the patient remained well for more than nine months. When his complaints recurred, the mediastinal skin portals showed a residual radiation effect too severe to permit further irradiation. The administration of HN2 was followed by remission of pain and dyspnea and regression of venous engorgement of the neck, lasting three and a half weeks. At the end of this period an experimental lead grid was devised to minimize the residual skin reaction. X-ray therapy was resumed and at the time of this report is approaching a cancerocidal dose, with much clinical benefit.

(d) In 15 of the 40 patients, the neoplastic disease was responsible, at variable intervals, for symptoms and signs of a systemic nature so severe as to preclude roentgen-ray therapy. The clinical picture at these intervals included extreme weakness, fever, night sweats, anorexia, and weight loss. Nine of the patients were so gravely ill that even transportation to the radiotherapy apparatus was fraught with

danger. A favorable clinical response was achieved with HN2 in 12 of this group, and definitive x-ray therapy became feasible in 6 instances.

CASE 5: A 64-year-old house painter received 6,000 r (depth dose) to the mediastinum for severe chest pain and intractable cough secondary to mediastinal extension of an anaplastic bronchogenic carcinoma (Fig. 2A). A remarkable clinical and radiographic response was observed (Fig. 2B), and the patient enjoyed a remission of six months with normal activity in a veterans' rest camp in the Adirondacks. He returned to the hospital complaining of abdominal pain and distention, jaundice, constipation, malaise, and weight loss of short duration. This clinical syndrome appeared to be the expression of metastatic neoplastic disease in the retroperitoneal nodes and abdominal organs. So seriously ill was the patient that even palliative irradiation seemed unfeasible. However, his systemic symptoms responded so readily to a single course of HN2 that we were encouraged to institute a course of radiation therapy to the abdomen. The response was again most gratifying, with relief of pain, regression of tumor masses, and even disappearance of jaundice for a month. This remission period was followed by the advent of intracranial metastasis and progressing abdominal cancer.

(e) Patients with compression of the

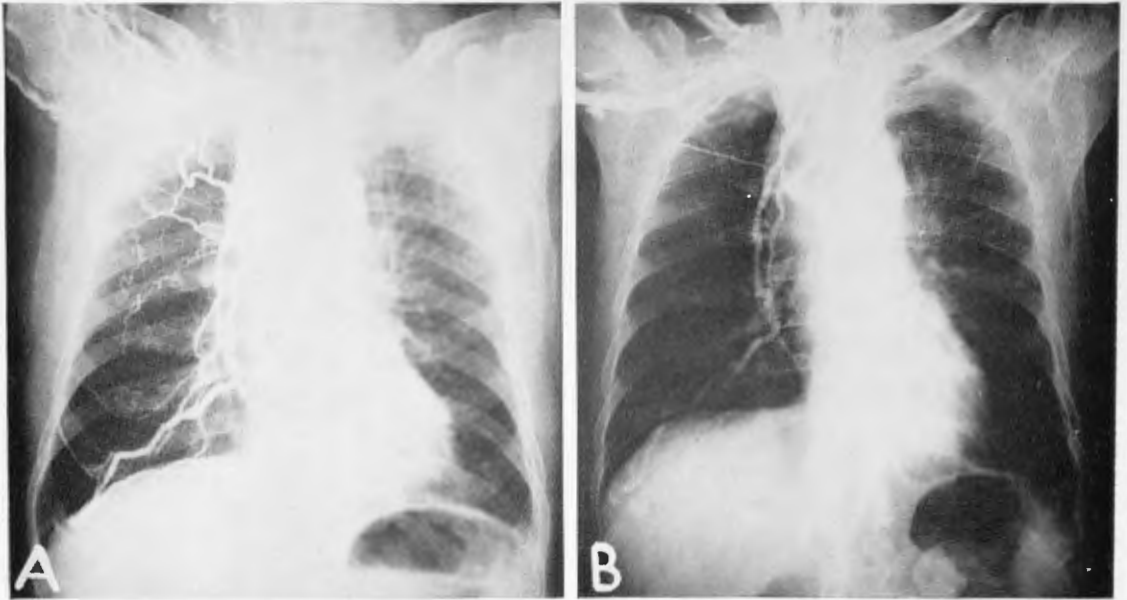


Fig. 3. Case 6. A. Angiocardiogram before HN2 therapy. Note block of the superior vena cava, with marked collateral circulation. The patient presented the clinical syndrome of superior mediastinal compression due to bronchial cancer.

B. Angiocardiogram after HN2 therapy, showing no significant change despite marked clinical improvement. Remission for seven weeks at home.

superior mediastinal structures due to bronchial carcinoma sooner or later will be in desperate need of relief from strangulation symptoms. Prior to January 1947, those patients who could be safely transported to the deep roentgen-ray apparatus generally benefited from daily fractional doses judiciously administered. Only terminal care could be offered those too gravely ill for transportation.

After January 1947, when HN2 was introduced, 9 patients with acute severe mediastinal compression were encountered, much too ill and dyspneic for transportation and too severely orthopneic for administration of deep x-ray therapy. Nitrogen mustard was given to all individuals in this group and 7 obtained immediate remissions. The clinical benefits of HN2 were often apparent before the course of four treatments was completed.

CASE 6: A 55-year-old veteran was admitted with the full-blown syndrome of superior vena cava compression secondary to bronchogenic carcinoma (Fig. 3A). The intensity of dyspnea, orthopnea, cyanosis, and swelling of the head and neck was most alarming. A course of HN2 produced complete relief

of strangulation symptoms and signs, with increase in weight, strength, and appetite. The patient was soon discharged from the hospital and remained well, at home, for seven weeks.

It is of interest that, in spite of the excellent clinical response, serial angiocardigraphic studies, made expressly for this purpose, showed little or no change in the obstructing neoplasm after nitrogen mustard therapy (Fig. 3B).

CASE 7. A 55-year-old veteran with classical signs of mediastinal strangulation secondary to oat-cell (anaplastic) bronchial carcinoma was almost completely relieved of dyspnea, orthopnea, edema of the face, cough, and chest pain after the first course of HN2. This remission lasted more than a month. Impressive objective evidence of favorable response was obtained in the form of infra-red photographs (Fig. 4A and B) and roentgenograms (Fig. 4C and D). The patient's difficulties recurred with greater intensity, but a second course of nitrogen mustard was of no avail.

(f) There were 6 patients with very far advanced pulmonary disease and generalized metastases in whom there was observed a prompt clinical response to HN2 that was quite unusual in some instances. The period of rehabilitation lasted from two weeks to two months, averaging 21 days.

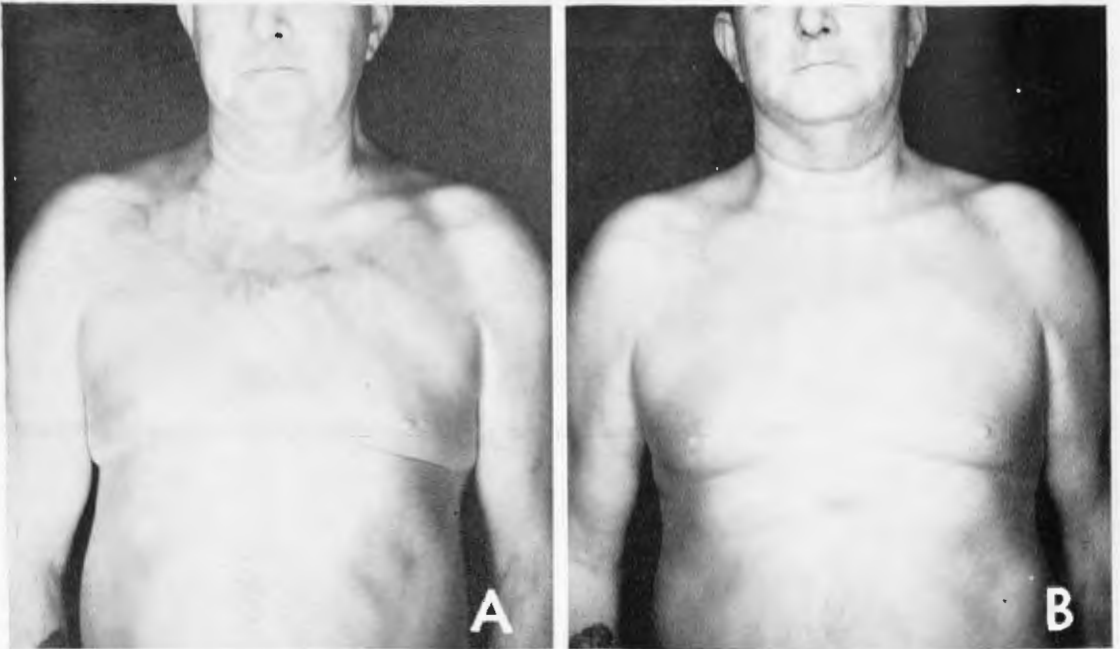
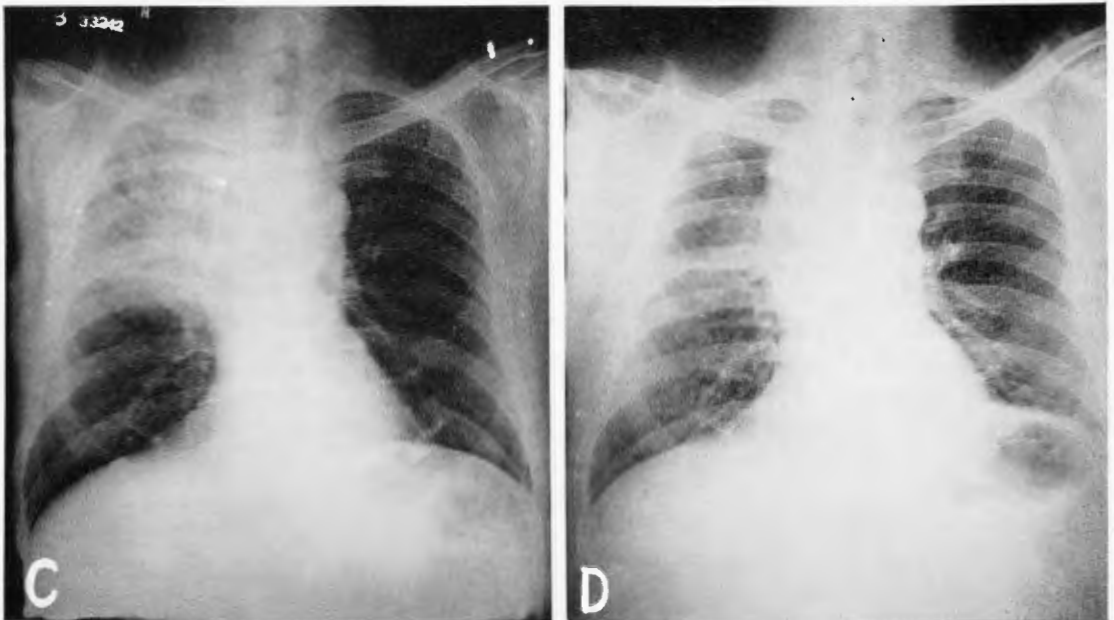


Fig. 4. Case 7. A. Infra-red photograph of a 55-year-old veteran with severe compression of superior vena cava by mediastinal tumor of bronchogenic origin. Note enormously dilated venous channels of chest wall.
B. Infra-red photograph obtained ten days after nitrogen mustard therapy, showing regression of dilated venous channels. This was associated with striking symptomatic benefit lasting one month.



C. Roentgenogram prior to first course of nitrogen mustard therapy. Note mediastinal mass and obstructive pneumonitis of right upper lobe.
D. Roentgenogram following mustard therapy. Note regression of pneumonitis. The mediastinal mass persists, however, despite clinical remission.
The infra-red photographs (A and B) appeared previously in the *American Journal of Roentgenology* and are reproduced here by permission.

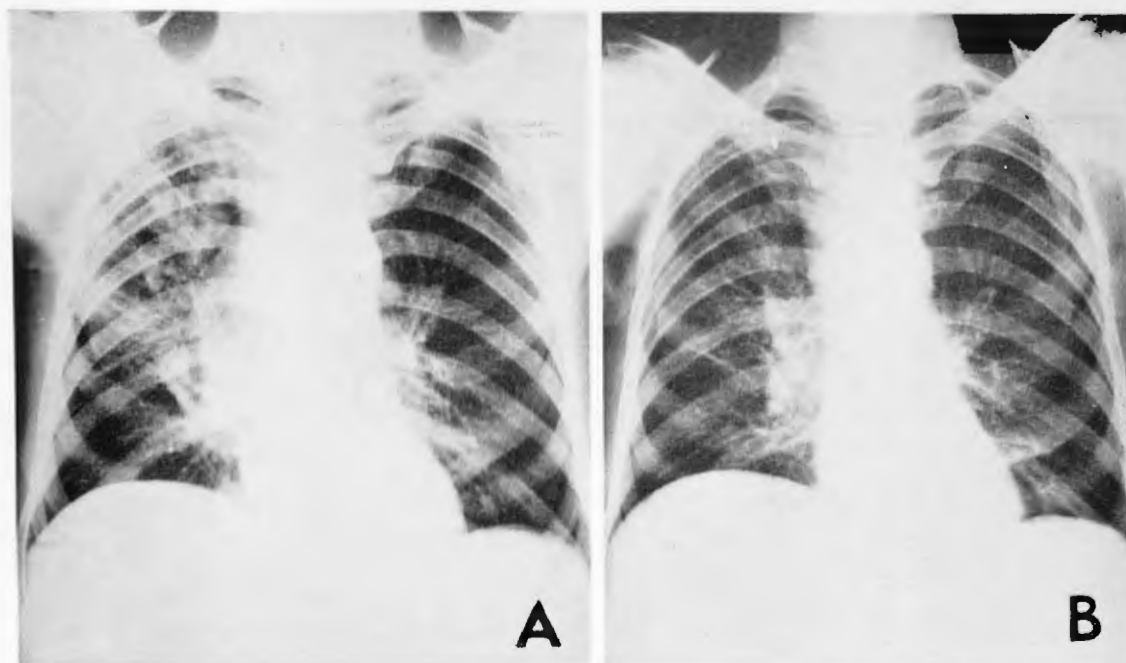


Figure 5. Case 8. A. May 10, 1948. Obstructive pneumonitis of right upper lobe, with mediastinal and hilar lymphadenopathy in a 49-year-old veteran with bronchial cancer. Superior vena cava compression and massive hepatomegaly. Patient extremely ill, almost "pre-terminal."

B. June 18, 1948, one month after nitrogen mustard therapy. Clearing of obstructive pneumonitis and diminution in lymph node involvement. Striking clinical improvement for one month.

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CASE 8: A 49-year-old Negro soldier was prostrated with far advanced anaplastic bronchial carcinoma associated with massive metastases in the liver, which distended the abdomen enormously. Dyspnea and orthopnea secondary to obstructive pneumonitis and compressing mediastinal nodes were most distressing (Fig. 5A). Although the case was regarded as "pre-terminal," nitrogen mustard was administered and a striking change was observed at the end of the four-day course. The liver receded fully 5 cm., the dyspnea and orthopnea were relieved through clearing of the pneumonitis (Fig. 5B), and the patient was able to get up and about without aid. He was comfortable and reasonably well till one month later, when his complaints recurred and intracranial metastases brought about his demise.

CASE 9: A 40-year-old veteran was found to be suffering from marked dyspnea, chest pain, fever, chills, anorexia, and marked weight loss. This was associated with atelectasis of the right lower lobe, metastatic deposits of anaplastic bronchogenic carcinoma in both lung fields, and extension of cancer to the mediastinal nodes (Fig. 6A). The patient was much too ill for anything but pre-terminal care. After a single course of HN2, there was regression of atelectasis, associated with remarkable clinical improvement, gain in strength and appetite, and relief of fever and dyspnea (Fig. 6B). This period of remission lasted two weeks. It is strange, however,

that, while the right lung field cleared, enlargement of metastatic deposits in the left lung was observed during the period of clinical remission.

No statistically valid conclusions regarding prolongation of survival time through the use of nitrogen mustard alone may be drawn from this series of cases. A few individuals treated in a pre-terminal state did gain a few weeks of comfortable life. In the opinion of other investigators (Table III) survival time does not appear to be appreciably prolonged.

DISCUSSION AND CONCLUSIONS

1. In this investigation, 40 patients with inoperable bronchogenic carcinoma received nitrogen mustard as a systemic adjunct to roentgen therapy when, in the opinion of the therapeutic radiologist, radiation appeared to be no longer feasible or effective. The specific indications for the employment of the drug have been described and illustrative case records cited.

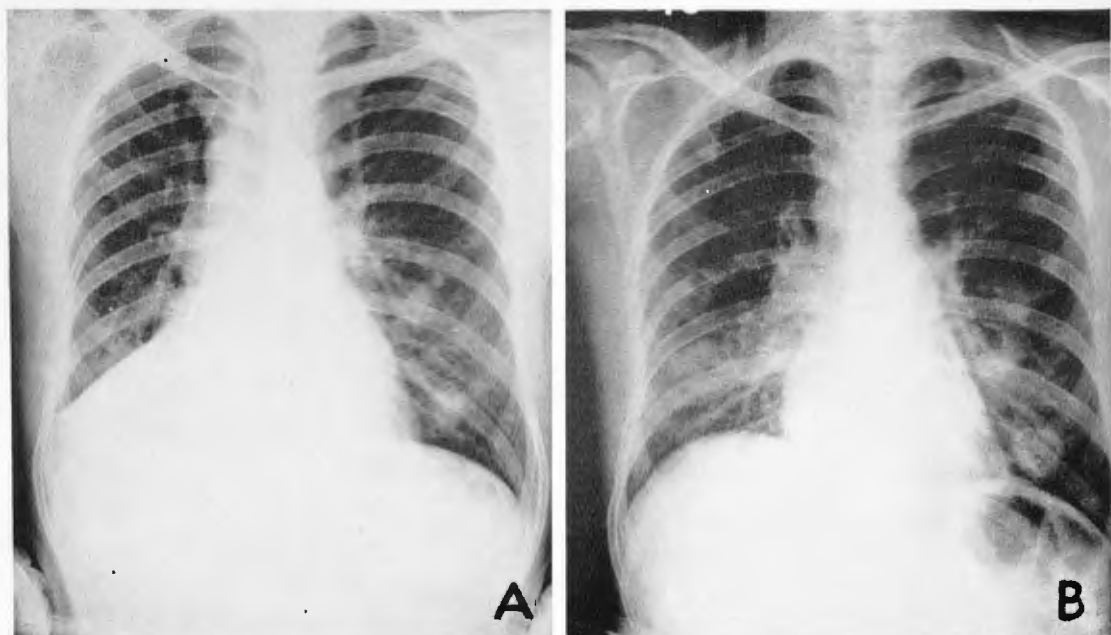


Figure 6. Case 9. A. Bronchial cancer causing atelectasis of right lower lobe, in a veteran aged 40 years, with metastatic deposits in both lung fields and in the mediastinal nodes. Marked dyspnea, pain, fever, chills and anorexia.

B. May 19, 1947, after HN2 therapy. Regression of atelectasis, associated with remarkable clinical improvement. Gain in appetite and strength and relief from fever and dyspnea. Note, however, enlargement of metastatic parenchymal deposits.

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TABLE III.: COLLECTED CASES TREATED WITH NITROGEN MUSTARD

Investigators	Total No. Cases	Favorable Response
1. Ariel, I. M., and Kanter, L. (2)	26	8
2. Ben-Asher, S. (3)	11	2
3. Bierman, H. R., <i>et al.</i> (4)	5	0
4. Boyland, E., <i>et al.</i> (5)	41	25
5. Faloon, W. W., and Gorham, L. W. (9)	5	0
6. Karnofsky, D. A., Abelmann, W. H., Craver, L. F., and Burchenal, J. H. (14)	35	26
7. Kent, L., and Reh, E. P. (16)	19	4
8. Kurnick, N. B., Paley, K. R., Fieber, M. H., and Adler, D. K. (17)	10	2
9. Lynch, J. P., Ware, P. F., and Gaensler, E. A. (19)	60	41
10. Shullenberger, C. C., Watkins, C. H., and Kierland, R. R. (25)	3	1
11. Skinner, E. F., Carr, D., and Denman, W. E. (26)	25	18
12. Videbaek, A. (29)	6	1
13. Wawro, N. W. (30)	4	4
14. Wintrobe, M. M., and Huguely, C. M., Jr. (32)	4	2
	254	134

2. Of the 40 patients, 30 enjoyed remissions of severe subjective symptoms and 19 experienced objective improvement as well. The remissions ranged from one to seventeen weeks, with an average of three and a half weeks. After a single course of the chemotherapeutic agent, it became possible to initiate effective radiotherapy in several patients apparently too seriously ill for *any* form of definitive treatment.

3. An exhaustive search of the literature has revealed a collective total of 254 cases treated with HN2 by 14 other investigative groups (Table III). In 134 of these cases (52.8 per cent) a favorable response was observed.

4. In our opinion, nitrogen mustard should never be employed as a *substitute* for radiotherapy in the presence of relatively localized inoperable bronchial cancer. Such patients should be given the benefits which local cancerocidal radiation can offer: longer remissions, prolongation of useful life for months or even years, and

a rare chance for cure. These conclusions are based principally upon (a) our control experience with 605 roentgen-treated patients, (b) a review of all mustard-treated cases thus far reported, and (c) 508 roentgen-treated cases from the literature (6, 18, 28, 31).

Leddy and Moersch, for example, indicated that 25 of 125 patients treated with deep roentgen-ray therapy lived from one to twelve years. Craver (6) reported a 5-year survival rate of 3.8 per cent in his series of roentgen-treated patients. Indeed, rapid advances now being made in new radiation technics, radiobiology, and mega-voltage engineering give promise of much more effective irradiation of deep-seated tumors.

5. In conclusion, we believe that nitrogen mustard, despite its limitations, will provide the therapeutic radiologist with a truly valuable adjunct to radiation in the management of inoperable bronchogenic cancer.

Acknowledgments: The authors wish to express their appreciation for the clinical services contributed by the Chest Sections of the Medical and Surgical Divisions. They are grateful, also, to the Medical Illustration Service for the quality of the illustrative material.

130 W. Kingsbridge Road
Bronx 63, New York

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SUMARIO

La Mostaza Nitrogenada como Coadyuvante de la Irradiación en la Asistencia del Cáncer Broncogéno

Cuarenta enfermos con carcinoma broncogéno inoperable recibieron mostaza nitrogenada como coadyuvante general de la roentgenoterapia cuando la última no parecía ser ya más factible o efectiva. Las indicaciones específicas para el empleo de dicha mostaza fueron las siguientes: (a) radiorresistencia de la lesión; (b) grave radiopatía; (c) agotamiento de las puertas cutáneas; (d) síntomas orgánicos intratables; (e) compresión mediastínica aguda; y (f) enfermedad avanzadísima. Presentáanse casos típicos de dichos estados.

En 30 de los 40 pacientes, el tratamiento con mostaza nitrogenada fué seguido de remisión de graves síntomas subjetivos, y en 19 de ellos se notó igualmente mejoría objetiva. Los períodos de remisión variaron de una a diecisiete semanas, promediando tres semanas y media. Después

de una sola tanda de mostaza nitrogenada, fué posible iniciar una roentgenoterapia efectiva en varios sujetos que previamente habían sido considerado demasiado enfermos para toda forma de tratamiento definitivo.

La mostaza nitrogenada no se recomienda como sustituto de la roentgenoterapia en presencia de cáncer bronquial inoperable y relativamente localizado. Esos enfermos tienen derecho a los beneficios brindados por la irradiación cancerocida local, o sean: remisiones más largas, prolongación de la vida útil por meses y posiblemente años, y hasta una probabilidad rara de curación. Sin embargo, esa mostaza sí aporta un valioso coadyuvante de la irradiación cuando ésta se ha vuelto ineficaz o está contraindicada por las razones expresadas.

