

Bari Harbor

—and the origins of chemotherapy for cancer

By Stewart F. Alexander, M.D.

In the last issue of CML, Army Chemical Review, we featured a story called, *The Mustard Fell Like Rain*, about the Bari, Italy, harbor disaster. You will remember that LTC Stewart Alexander was the physician dispatched by the Allied Command Surgeon to investigate the mysterious deaths. Dr. Alexander was contacted and agreed to do a follow-up story for us. —Editor

The use of chemotherapy for treatment of malignant disease ranks as one of the great developments of the 20th Century. Chemical warfare has been castigated throughout this century as an evil and destructive force. Contributions of chemical warfare research to the benefit of mankind are rarely understood or even mentioned. This article approaches just one of these remarkable relationships.

The Medical Research Laboratories of the United States Chemical Warfare Service at Edgewood Arsenal, Maryland, was under the command of COL William D. Fleming prior to and in the initial stages of the United States' entry into World War II. It was organized into two main divisions—toxicology and medical. Dr. Howard Skipper (who later achieved fame in cancer research and who served as Director of the Southern Research In-

stitute) headed the toxicological section. I headed the medical section. (I later became consultant in Chemical Warfare Medicine to the Allied Force Headquarters under General Dwight D. Eisenhower). Among the multiple responsibilities of the two sections was the study and appraisal of known and unknown chemical agents.

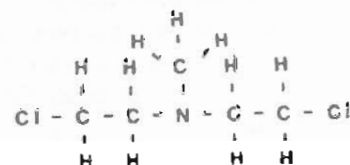
Early in 1942, samples of two agents (smuggled out of Germany by unknown but brave individuals) came under study. It was believed the agents were studied and possibly produced in Germany. The initial toxicological evaluation by Dr. Skipper identified the agents as vesicant and highly toxic. Analysis by him proved that the agents were N-methyl-2,2' dichloro-diethyl-amine and 2,2',2" trichloro-triethyl-amine.

Arbitrarily labeled 1060 and 1130, they were turned over to the medical section for further evaluation. Later, it was ascertained that one of the compounds had been known by the Chemical Warfare Service in 1935, but had been rejected without study or knowledge of its physiological effects, except for its vesicant action.

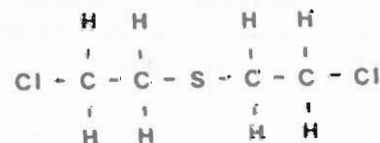
We immediately initiated detailed research studies of their effects on all the major organ systems and verified their potent vesicant action on the skin, eyes, and respiratory track.

Their most amazing additional effect was on the hematopoietic system (blood and blood-forming organs). We had never before seen such rapid destruction of white blood cells nor the destruction of lymph nodes and bone marrow elements.

The observations were so shocking that all tests were repeated to rule out poor animal stock or species sensitivity—but the effects were always present and reproducible. Because their chemical structure—



resembled the chemical structure of conventional mustard gas—



the term nitrogen mustard was proposed, and studies continued to further understand the hematopoietic effects of these agents. Because of the dramatic and

reproducible effects of these agents, the possibilities of using them directly or in modified forms in the treatment of leukemia and other malignant lympho-hematogenous disease was presented.

Consultation with hematology experts was sought, but was handicapped by the high degree of security imposed. National security limited our access to many brilliant minds. Furthermore, we were instructed that our responsibilities were solely to support the war effort and that other collateral lines of investigation could not be pursued at that time.

Consultations were permitted with Dr. Milton Winternitz who had full clearance as a member of the National Research Council (NRC). Dr. Winternitz, a most distinguished pathologist who had been a senior investigator in chemical warfare medicine in World War I, had the widest experience in these fields. He had edited and written sections of the definitive text on the pathology of mustard gas and other war gas poisoning. His book stood as a classic and the authoritative reference. Dr. Winternitz was internationally recognized and was at that time Dean of the Yale University School of Medicine.

The bizarre blood findings were discussed with him at length. Observations such as these were not described in his experimental work or in his book, and he stated that such findings had not been seen in the multitude of mustard gas poisoning cases in World War I. Initially, he doubted their validity and felt that these effects did not occur in humans.

Because of my concern with our observations, I unofficially traveled to New York City to consult Researcher and Professor of Medicine, Franklin Hanger, at the Columbia University College of Physicians and Surgeons. [Dr. Hanger later became



The harbor at Bari, Italy

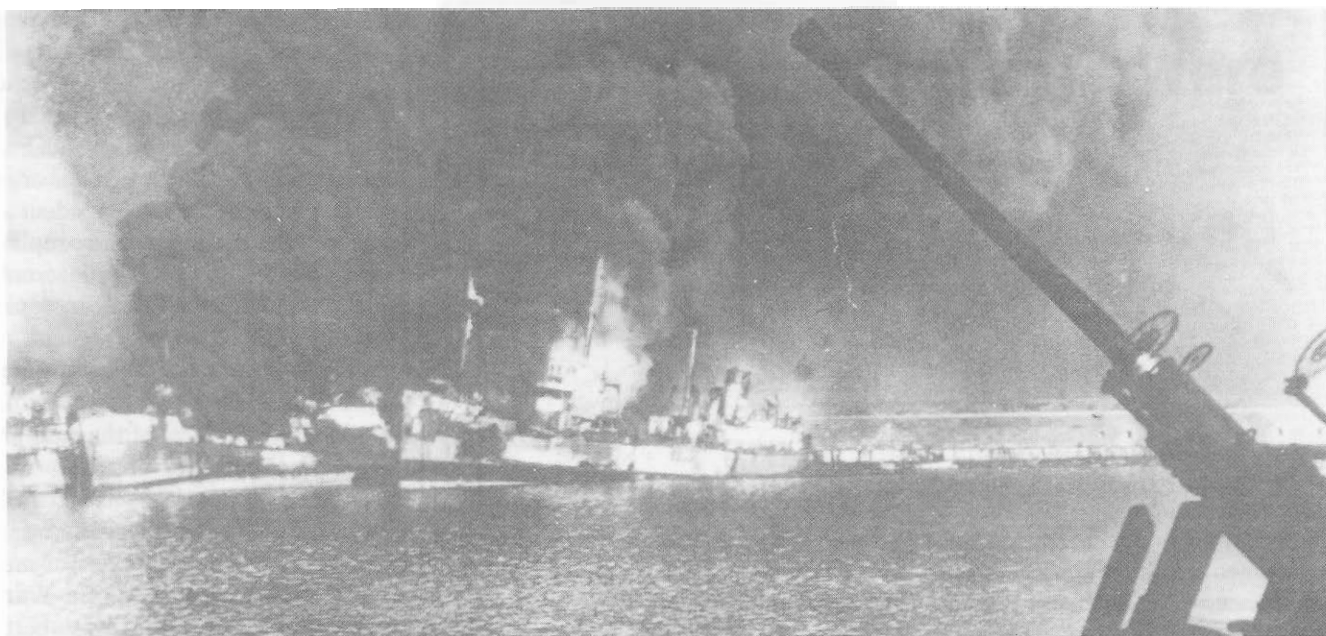
the President of the American College of Physicians.] Because he was not cleared at that time for highly classified information, I spoke with him only in terms of coded compounds. I could not and did not break my high security level. After reviewing raw data, Dr. Hanger stated that if such a compound existed, he would give anything to have samples for study of its possible usefulness in treating lympho-hematogenous malignancies in his laboratories. Unfortunately, I could not provide Dr. Hanger with samples nor could I reveal the identity of the compounds, but his enthusiasm was reassuring.

Dr. Winternitz did receive samples and presumably made them available to co-workers at Yale University, who subsequently reported their findings. The original research was published as MDEA 59, *Preliminary Report on Hematological Changes in the Rabbit Following Exposure to Lethal Doses of 1130* and establishes the date (June 11, 1942) and priority of these findings.

MDEA 59 was classified and had a classified distribution of 21 copies. In subsequent clinical and basic science studies, no references were

made to the original descriptions or to the men who participated in the original studies. T. W. Kethley, C. B. Marquand, O. E. McElroy, B. P. McNamara, G. A. Neville, and H. C. Michel were thus denied any recognition. My recommendations that further studies to evaluate the application of these compounds in the treatment of malignant lympho-hematogenous diseases by the NRC be continued under the aegis and leadership of the Medical Research Laboratories were not implemented. And there the matter hung.

With the buildup of American troops in England and the planning for Allied offensive actions, General Dwight D. Eisenhower requested of General George C. Marshall that a medical officer well-versed in chemical warfare be assigned to his headquarters. As Torch operation planning began, I was assigned to General George S. Patton's Western Task Force Headquarters to be detailed later to General Eisenhower in North Africa. (I was a MAJ at that time, but later was promoted to LTC). I was appointed Consultant in Chemical Warfare Medicine to the Allied Force Headquarters with responsibilities to American and



Ships burn in the harbor at Bari, Italy.

British forces.

In due time, North Africa was cleared, control of the Mediterranean reestablished, Sicily conquered, and the campaign for Italy begun.

By December 1943, American and British troops advanced north on the western side of the Italian boot, and the British (under General Bernard Montgomery) advanced on the eastern or Adriatic shores of Italy. The entire eastern portion of Italy lay exclusively under British control except for the Foggia airfields. The port of Bari was the main support and supply base for the British 8th Army and for all British forces. It was a small port, overcrowded and overworked.

On the evening of 2 December 1943, the German Luftwaffe, after daily surveillance of the port activity, attacked with 105 twin-engine JU-88 bombers. The port had no effective defense and the attack was devastatingly destructive (photo, above). Sixteen ships were sunk and four others damaged. It was the largest naval port disaster of the war except for Pearl Harbor. We must remember that the Pearl Harbor attack was

launched before a declaration of war, while the Bari Harbor attack occurred in an active war zone. Casualties were high and the British, New Zealand, and Indian hospitals, already caring for battle casualties, were overwhelmed.

Wounded men, blast injuries, and fire burns received priority of treatment. Many of the men rescued from the water and covered with harbor oil were wrapped in blankets, kept warm, given warm drinks, and left to rest while the more seriously injured were being treated. During the next two days medical officers were startled that these presumably non-injured men suddenly died. By the second day, British medical officers became alarmed as these strange deaths increased and they feared that some new chemical poison had been introduced. A panic call to Allied Force Headquarters resulted in my being flown immediately to Bari.

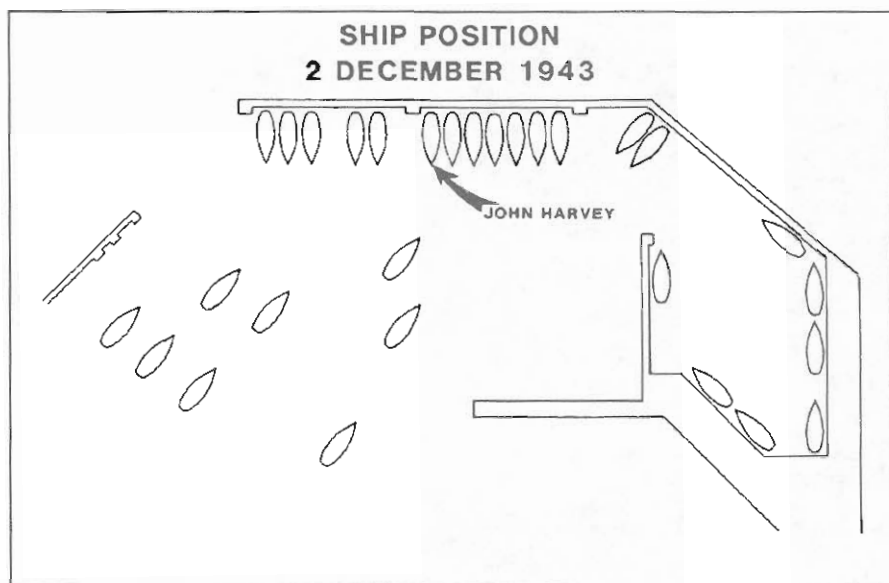
After initial inspection and examination, I stated that many of the casualties appeared to be due to mustard gas poisoning and ordered careful testing of those casualties still alive and complete and careful

autopsies of those casualties who died under these strange circumstances.

Under questioning, the British authorities stated categorically that there was no mustard in the area and that if mustard was present, it could only have come from German planes. The politico-military significance of such a statement and conclusion was awesome. A rapid study and outline of the location where these unusual casualties occurred made a German airborne delivery most unlikely, and the British authorities were carefully questioned again.

Everyone, including the post commander, denied the presence of American or British mustard gas. A study of casualty distribution (photo, page 24) indicated that an American cargo ship, *John Harvey*, was the focal point of the casualties and that this ship no longer existed. It had been completely blown to pieces.

A frogman, searching the bottom of the harbor in the area, recovered a bombshell fragment with clear markings: M47A1, identifying it as an American 100-pound mustard gas bomb. Confronted with this evi-



Ship positions in the harbor at Bari, Italy.

dence, the British Port Commander acknowledged that the *JohnHarvey* was transporting 100 tons of mustard gas in addition to many thousands of tons of high explosive. He also stated that he had been on explicit orders to deny the presence of mustard gas. All members of the detachment of the 701st Chemical Maintenance Company, commanded by 1LT Howard D. Beckstrom and detailed aboard the *JohnHarvey* to service the mustard gas bombs, had been killed in the catastrophe and were unable to give a gas alarm.

I then framed the following picture of what had happened. Of the 100 tons of mustard blown up, much was destroyed in the terrible fires present. Large portions were hydrolyzed by the salt water and rendered inactive. Some vapors were blown out to sea by an offshore wind that was present. But the mustard taken up by the harbor oil formed a solution of mustard gas in oil that covered these unfortunate casualties. Those who washed off the oil from their bodies sustained minimal or no injuries. Those who did not died.

The first aid treatment given would have been correct for usual immersion, but wrapping the men in

blankets for warmth permitted the absorption of mustard gas through the skin, leading to severe systemic poisoning. Injuries due to vapor occurred but were not of major degree or significance except in the case of the US destroyer, *Bistera*, on patrol duty. The offshore wind carried mustard gas vapors that inflamed the eyes of most of the crew, requiring the temporary berthing of the ship at Taranto. No gas alarm was given, although members of the crew had complained of the garlic odor that they attributed to the eating habits of the local population!

In mid-1943 there had been a significant movement of German chemical weapons into the Italian war theatre. In response to this, the President of the United States issued a strong warning in August 1943 that any use of chemical agents by the Axis Powers would bring an immediate heavy retribution: "Any use of poison gas by an Axis Power, therefore, will immediately be followed by the fullest retaliation." The political significance as well as the military significance of any error in interpreting the factor of and source of mustard gas in Bari was horrendous.

After my initial judgment, I in-

itiated high priority messages through Allied Force Headquarters to the President and to the Prime Minister of England, informing them of the nature of this group of casualties and of the almost certain origin of the mustard gas. The President accepted the findings and replied, asking that he be kept fully informed. The Prime Minister, however, denied that any mustard gas was present.

A most unusual exchange of messages then took place with my detailing all the facts of the case and the Prime Minister insisting each time that my appraisal was incorrect. The Prime Minister stated that he had seen thousands of cases of mustard gas poisoning in World War I and inferred that he was better versed in the field. He, of course, had never encountered exposures from mustard in oil.

Under great danger of court martial, I replied that if the Prime Minister could not accept the medical judgments made, he was free to make his own diagnoses. The matter culminated with the directive of the Prime Minister that all references to mustard gas or to the Consultant in Chemical Warfare Medicine be removed from all British records, medical and otherwise. He directed that these casualties be diagnosed as "burns due to enemy action" or "NYD" (not yet diagnosed); and so they remain to this day.

In my compilation of data (as the consultant) prior to the Prime Minister's edict, this group of casualties was separated from those suffering wounds, thermal burns, blast injuries, or other evidences of trauma. This group numbered 617 cases, of whom 83 died.. We obtained complete autopsies and duplicate samples of all tissues. One set of pathology specimens with attached medical records was dispatched to Edgewood Arsenal, and an exact duplicate was dispatched to Porton, England (the

British Chemical Warfare Research Center). No acknowledgment of the receipt of the data or pathology specimens by Porton was ever made.

During this period of turmoil, blood studies and clinical observations convinced me that I was seeing in human beings the very thing I had demonstrated in my laboratories at Edgewood Arsenal. The difference in this group of casualties and those in World War I was that significant amounts of mustard were absorbed through the skin from contact with the mustard in harbor oil. Relatively little mustard gas vapors were inhaled and the massive pulmonary congestion seen in World War I only minimally present.

Thus, the systemic effects of mustard were more clearly seen. Mustard gas did, in truth, selectively destroy blood cells and blood-forming organs when the massive exposures of wartime occurred. These observations (which could have been made and should have been made in World War I) now verified the data demonstrated at Edgewood Arsenal Medical Research Laboratories. Subsequent search of the literature revealed that observations similar to those described were reported in separate papers in 1919 and 1920, but were misinterpreted as due to secondary infection. These reports were never followed up and were not included in Dr. Winternitz's text.

No official acknowledgment of the receipt of the preliminary report or of the final report of the Bari Harbor Disaster was ever made by either the American or British Command because of the absolutely negative stand taken by the Prime Minister. Official recognition by the United States Government was finally made in 1988 and then only through the literary research, writings, and diligent persistence of Nicholas T. Spark, a high school student, of Tucson, Arizona, supported by the

"...medical officers were startled that these presumably non-injured men suddenly died."

understanding, compassion, and fairness of United States Senator Dennis DeConcini of Arizona and United States Senator Bill B. Bradley of New Jersey.

However, private and unofficial praise for the data and its evaluation were rapidly forthcoming from senior members of the medical service and of the Chemical Warfare Service, including GEN Frederick Blesse, senior American medical officer at Allied Force Headquarters and GEN Charles S. Shadle, chief chemical warfare officer at Allied Force Headquarters. Dr. Cornelius P. Rhoads, chief of the medical division in the office of the chief of the Chemical Warfare Service in Washington was immediately aware of its significance and applauded the report saying, "I would like you to know of the high praise that has been given your report on the Bari Disaster. It provides us with such complete information as to represent almost a landmark in the history of mustard poisoning."

Dr. Rhoads was a tower of strength in reopening and pursuing the medical application of mustard gas compounds in the treatment of human cancer. Dr. Howard Skipper, at the Southern Research Institute, developed magnificent concepts and techniques in advancing knowledge of malignant cell dynamics, of cell growth and doubling time, and of

cancer treatment appraisal. Mechanisms of treatment and chemical modifications of the compounds followed in steady progression. As organizer and director of the Memorial Sloan Kettering Institute, Dr. Rhoads led the way in joining new approaches to the treatment of cancer. The initiation of all these phases of chemotherapy for the treatment of human cancer has been dated from the time of the Bari Harbor observations.

As experimental data in the United States verified the great potential of the nitrogen mustards, chemical derivatives of the initial amines expanded the clinical use of chemotherapy. The magnificent inductive thinking of men like Dr. Sidney Farber of Boston, who reasoned that if one chemical compound could attack malignant disease there must be others, produced a major advance in developing and proving methotrexate. Centers for the study and treatment of cancer developed in major cities throughout the United States and around the world.

Subsequently, other chemical compounds and other new antimetabolite drugs have been developed and an entirely new subspecialty of medicine has been created in the field of Oncology.

Today, chemotherapy stands with surgery and radiation as one of the

three major therapeutic measures in the treatment of cancer, with slow but ever-increasing evidences of effectiveness. Current research is ever-widening. In the search for more information, molecular, biological, and immunological techniques do hold promise for further advances. Genetic, biogenic, cellular, and sub-cellular studies open deep knowledge of normal and malignant cell function and growth and one day hopefully will lead toward reducing the incidence of or preventing the development of some types of can-

cer.

That chemical warfare was the focal point in initiating and directing this course of knowledge enhancement is an honorable state deserving of recognition by the peoples of the world. Indeed, it draws strength from the clarion injunction of the ancient prophet, Isaiah, as he calls loud and clear from the depths of war experiences for the hope and salvation of man:

"And they shall beat their swords into plowshares and their spears into pruningforks."

Clearly this has been done.

Dr. Stewart F. Alexander has a BA from Dartmouth College and an MD from Columbia University College of Physicians and Surgeons. Throughout his professional career, Dr. Alexander has chaired and been a member of numerous professional organizations. He instructed at the New York School of Medicine (1946-1961) and the Columbia University College of Physicians and Surgeons (1952-1965). He is the recipient of many military awards, to include the Bronze Star Medal, the American Defense Medal with Foreign Service Clasp, the EAME Medal with Seven Battle Stars, the D-Day Arrowhead, and the Victory Medal. Dr. Alexander lives in Park Ridge, New Jersey.

HBO Helps Leadership Training

The United States Army's Training and Doctrine Command has directed that leadership assessment become a requirement in all resident leader training courses. As a part of the United States Army Chemical School's officer and NCO professional development education system, the Center for Army Leadership (CAL) Leadership Assessment Development Program (LADP) has been instituted to assess FM 22-100 leadership competencies of our students.

We reviewed numerous movies and television programs to determine suitable scenarios to train interrater reliability on the assessment forms. We found suitable practice scenarios in the Home Box Office (HBO) *Vietnam War Story* series that met our subject matter and length of presentation.

We contacted HBO to obtain permission to use the *Vietnam War Story* series in facilitating our leaders' education. Ms. Ellen Ginsburg, Associate Director for Business Affairs, West Coast Home Box Office, Inc., granted permission to the US Army Chemical School "for the sole and express purpose of education, i.e., teaching

evaluation in your Leadership Assessment Program to evaluate the leadership potential of its officers and non-commissioned officers."

HBO provided the following episodes of *Vietnam War Story*:

- Home
- The Pass
- Dusk To Dawn
- Fragging
- An Old Ghost Walks the Earth
- The Mine
- R&R
- Separated
- The Promise

This critically acclaimed series has been cited for its attention to detail and realism. It provides the US Army Chemical School with examples of various levels of leadership positions and multiple opportunities for use as practical exercises to record, classify, and rate behaviors.

Dr. Charles E. Notar, US Army Chemical School Master Assessor and trainer of assessors, states that the HBO series has been well received and is better at providing assessment training opportunities than originally thought.