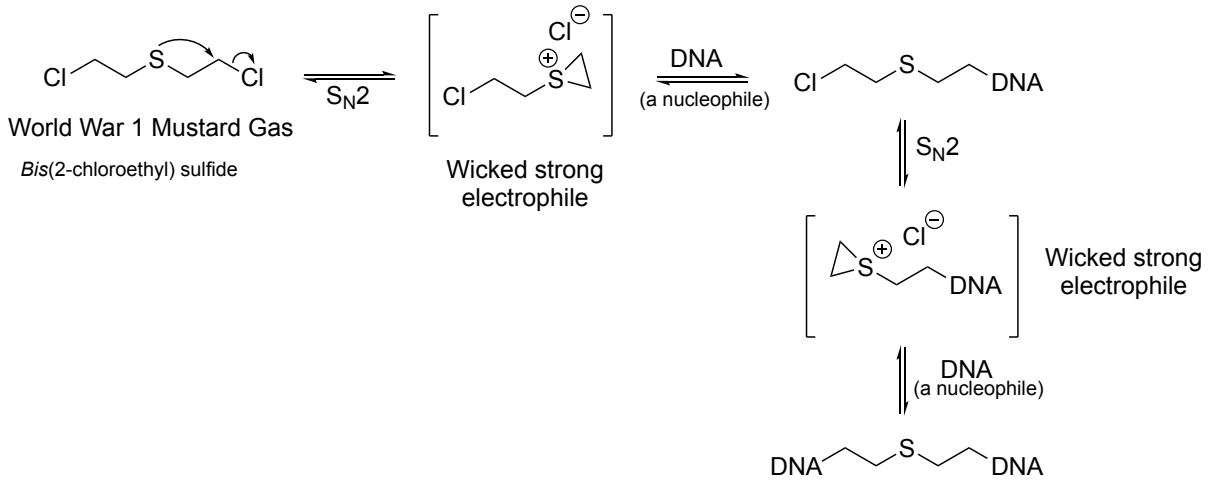
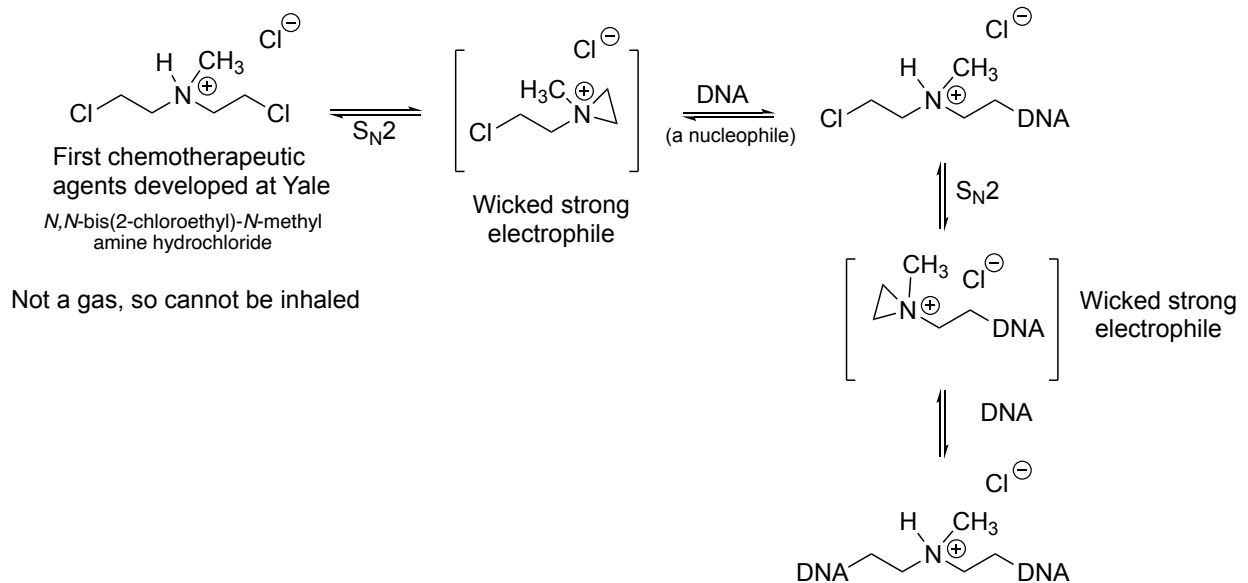




↑ Reacts with numerous nucleophiles leading to massive tissue damage in lungs when gas is inhaled, killing soldier



Crosslinked DNA that cannot replicate, killing fast dividing cells - observed to be immune system cells and hair cells in soldiers who survived mustard gas exposure on the World War 1 battlefields.



Crosslinked DNA that cannot replicate, killing fast dividing cells including cancer cells, but also immune system cells and hair cells.

The origins of chemotherapy are closely tied to the large-scale industrialization of chemical warfare in the early 20th century:

The conceptual foundation of modern chemotherapy emerged from the observation that certain chemicals could differentially damage rapidly dividing cells. Before World War I, pioneering work by Paul Ehrlich on arsenical compounds such as arsphenamine (Salvarsan, $C_{12}H_{12}As_2N_2O_2 \cdot 2HCl \cdot 2H_2O$) for syphilis and by Gertrude and Carl Voegtlin on folate antagonists had already established the idea of “magic bullets” that target specific biological processes. However, these early agents were primarily directed against infectious diseases, not cancer. The decisive turn toward antineoplastic chemotherapy required a tragic “experiment” in humans and animals: large-scale exposure to vesicant and alkylating agents used as military poison gases.

World War I mustard gas (bis(2-chloroethyl) sulfide, $C_4H_8Cl_2S$) provided the critical mechanistic link between chemical warfare and cancer therapy:

During and after World War I, clinicians and pathologists examining victims of sulfur mustard gas attacks noted profound bone marrow and lymphoid tissue suppression, characterized by leukopenia and lymphoid atrophy. Sulfur mustard, a bifunctional alkylating agent, forms highly reactive aziridinium intermediates that attack nucleophilic sites on DNA, especially at the N7 position of guanine, causing crosslinks, strand breaks, and ultimately cell death in rapidly proliferating cell populations. These observations led investigators to hypothesize that chemically related compounds might selectively kill rapidly dividing malignant lymphoid cells. The concept that deliberate administration of an alkylating agent could be exploited therapeutically emerged directly from autopsy and hematologic findings in mustard gas casualties, effectively transforming an indiscriminate battlefield poison into a prototype for targeted, dose-controlled pharmacologic intervention.

The first modern chemotherapy trials used nitrogen mustards, structurally related to sulfur mustard but with an N,N-bis(2-chloroethyl) amino core:

In the early 1940s, work at Yale and elsewhere focused on nitrogen mustards, such as mechlorethamine (mustine; N,N-bis(2-chloroethyl)-N-methylamine hydrochloride, $C_5H_{11}Cl_2N \cdot HCl$), which share the same bis(2-chloroethyl) alkylating functionality as sulfur mustard but replace the sulfur atom with nitrogen. Classified as chloroethylamine derivatives, these compounds cyclize to aziridinium ions that DNA-alkylate in a similar fashion. Covert clinical experiments in patients with advanced non-Hodgkin lymphoma demonstrated rapid, though transient, reduction in tumor burden

and improvement in symptoms after intravenous mechlorethamine administration. The dramatic but short-lived responses in these early patients, treated under wartime secrecy due to the compounds' military origin, are widely regarded as the birth of systemic cytotoxic chemotherapy for cancer.

From nitrogen mustards to a pharmacologic arsenal: the “poison gas” concept generalized into rational anticancer drug design:

The success of mechlorethamine spurred development of a broad class of alkylating agents and antimetabolites that built on the same fundamental principle: exploit biochemical vulnerabilities of rapidly dividing cells. Additional nitrogen mustards such as cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P$), chlorambucil (4-[4-bis(2-chloroethyl)amino]phenyl butanoic acid, $C_{14}H_{19}Cl_2NO_2$), and melphalan (4-[4-bis(2-chloroethyl)amino]phenylalanine, $C_{13}H_{18}Cl_2N_2O_2$) extended the chemical logic while improving pharmacokinetics, tissue distribution, and therapeutic index. In parallel, folate antagonists such as aminopterin and later methotrexate (4-amino-10-methylfolic acid, $C_{20}H_{22}N_8O_5$) translated biochemical pathway inhibition into effective leukemia treatments. Together, these developments transformed the lethal lessons of sulfur mustard (bis(2-chloroethyl) sulfide) into a rational framework for anticancer drug discovery, in which highly reactive electrophiles and pathway-targeted antimetabolites are harnessed, in carefully controlled doses, to eradicate malignant cells that share the proliferative vulnerabilities first revealed by battlefield toxicology.