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The toxic action of dichlorethylsulphide (" mustard gas ").

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The investigations recorded in these two papers are founded upon numerous series of animal experimentations and also clinical observations of human mustard gassing.

1. *Local Action: Skin.*—Dichlorethylsulphide ("mustard gas"), in liquid or in vapor form, even in very low concentrations, is an escharotic poison for the animal tissues (skin, conjunctivæ, cornea, mucous membranes of respiratory and gastrointestinal tracts) with which it comes in direct contact. The degree of the injury is proportionate to the concentration of the gas, the time of exposure, individual susceptibility, and local physical conditions, such as moisture, sweating, warmth, pressure and friction. The escharotic action is, for the greater part, painless, the anesthetic effect being especially notable upon the skin; while upon the mucous membranes its action may be more irritant, probably chiefly reflex in character. The cutaneous surfaces most susceptible are those with thinner, more delicate skin, well supplied with sweat glands and hair follicles, where sweat may collect, and which are exposed to friction or pressure, such as the axillæ, flexor surfaces, genitals, inner surface of arms and corresponding surface of trunk, inner surfaces of thighs, between the fingers, etc. There is a penetration of the gas into the sweat and sebaceous glands, and a re-solution of mustard gas vapor into the sweat or sebum occurs. The injuries are particularly striking in their insidious, slowly progressive development, becoming first apparent only some hours after the exposure. Upon human skin the lesion appears as a hyperemia, followed by vesication, eschar formation, sloughing and slow healing, with more or less pigmentation. Depilation may occur; in severe cases the eschar may extend entirely through the corium into the subcutaneous tissues. Secondary infection and gangrene of the eschars occur invariably

in cases not properly treated. Milder lesions may show only the earlier stages of hyperemia, vesication or pigmentation. In general the injuries may be classed as burns of first, second or third degree. Following extensive hyperemias in human skin a most marked pigmentation, exceeding in degree the most marked forms of solar tan may be quickly developed and fade slowly. This pigmentation may be diffuse or spotted. In human skin vesication is pronounced; in animals the cutaneous lesions are characterized by the development of marked subcutaneous edema in the injured area. The fluid of the vesicle or of the edema is nonirritating when applied to uninjured areas. In the case of human skin frequently exposed to very dilute concentrations (only perceptible by odor), an eczematous itching condition between the fingers, on the genitals, etc., may develop; rubbing or scratching of the itching part may lead to the quick development of a blister or superficial eschar (*Nikolsky's sign*). Such interdigital lesions in laboratory workers may resemble clinically those produced by the itch mite. Cutaneous areas injured by mustard gas are rendered more susceptible to trauma or other forms of injury, including new exposures to mustard gas. This local susceptibility is, however, a general one, and not a specific lowered resistance to the action of dichlorethylsulphide. Subcutaneous injections of pure dichlorethylsulphide produce painless eschars, followed by dry sloughing, with edema less marked than in the case of external cutaneous application; a hypostatic edema may develop on the animal's belly when injected in the back. In the tissues at the site of the injection and in the hypostatic edema mustard gas may be present for some days after the injection, as shown by odor and physiological reaction. The resolution of mild skin injuries is often attended by troublesome itching. Healing of the deep cutaneous eschars is very slow; during the healing of extensive deep lesions the patients complain of a sensation of tightness or contraction of the skin; large scars may be produced resembling those resulting from deep thermal burns. The hair may be lost; but when regenerated they may be white in color.

Eye.—Upon the cornea mustard gas exerts an especially injurious action, particularly at the vertex. Within ten to fifteen

minutes after exposure to dilute concentrations, degeneration or necrosis of the corneal surface may be demonstrated by the application of a 2 per cent. alkaline aqueous solution of fluorescein, the injured cells retaining a greenish fluorescent coloration. In more severe injuries the cornea may be killed throughout its entire thickness at the vertex. The mildest cases show a slight cloudiness; the severe cases present a characteristic porcelain appearance of bluish white opalescent cloudiness, often with a more opaque band or line running horizontally across the cornea just below its transverse diameter. The injury to the conjunctiva is shown by the development of a more or less severe catarrhal, seropurulent or purulent conjunctivitis with marked edema of the subconjunctival tissues leading often to "ruffling" of the lids, entropion, ectropion or a combination of these. Even the lighter cases tend to run a chronic course with disturbances and reduction of vision. In the severe cases cicatrization and vascularization of the cornea take place slowly with resulting impairment or loss of vision. The injured eye is more susceptible to infection; and in infected cases suppurative panophthalmitis may develop with complete destruction of the eyeball. Recovered cases of mild mustard gas conjunctivitis often show an increased sensitivity to the action of light, dust, and other irritants, including mustard gas fumes.

Respiratory Tract.—Upon the mucosa of the respiratory tract mustard gas vapor produces a local injury to the epithelium as shown by the development of a catarrhal, desquamative, membranous, diphtheritic or purulent inflammation (rhinitis, stomatitis, pharyngitis, laryngitis, tracheitis and bronchitis), these lesions being most severe in the nose, back of tongue, palate, pharynx and larynx, decreasing in intensity downwards. Coryza, salivation, dryness of mouth and throat, aphonia and persistent cough are the chief symptoms, with physical signs of laryngeal, tracheal and bronchial involvement, and atelectasis, emphysema and edema of the lungs. As a result of secondary infection a purulent bronchopneumonia may develop.

Gastrointestinal Tract.—Through the swallowing of air, saliva or secretions from the upper respiratory tract containing mustard gas, or from the ingestion of contaminated food local corrosive action upon the alimentary mucosa may be produced, varying

from a catarrhal inflammation to large areas of eschar formation with resulting gastric ulcer, perforation, etc. The symptomatology of the mildest lesions is covered up by that resulting from the more severe burns elsewhere; the more severe ones will produce marked symptoms referable to the stomach and intestines.

2. *General Action: Susceptibility.*—There exists a racial (whites more susceptible than negroes) and an individual susceptibility to the action of dichlorethylsulphide, particularly in the case of the skin and probably also of the respiratory tract. The individual susceptibility, in some cases at least, is associated with the characteristic stigmata and symptomatology of the thymicolymphatic constitution. Acquired susceptibility is not specific. Animals show also generic and individual differences in sensitivity to mustard gas.

Systemic Action.—There is no evidence of any systemic poisoning by the absorption of dichlorethylsulphide from the skin, eyes or mucous membranes of the respiratory or gastrointestinal tracts. There is no metastatic action of the gas from the site of local external application.

Shock.—In all severe cases of mustard gas burns of skin, eyes, or mucous membranes there is usually the clinical picture of severe shock, in the form of intense pallor, depression of pulse and temperature, general collapse, nausea and vomiting. The mildest cases show no systemic reaction.

Blood and Urine.—No changes are observable in the blood or urine of mild cases. In cases with large infected burns of skin or respiratory tract, the blood presents a mild secondary anemia with leucocytosis; we have never observed leucopenia; the blood urea is increased; the urine is diminished, concentrated, and contains casts and albumin. Under forced fluids the urinary symptoms improve, and the blood urea diminishes. In severe infected cases the general picture may be that of a severe toxemia.

Intravenous and Subcutaneous Injection.—When injected intravenously or subcutaneously dichlorethylsulphide is an active poison, causing death in one to four hours intravenously and two hours to three weeks after subcutaneous injections (for rabbits intravenous injections of .0075 c.c. per kilo may be lethal within four hours), according to size of dose, individual animal, etc.

When death takes place quickly, the symptoms are chiefly those of an action upon the central nervous system, such as hyperexcitability, rapid respirations, general convulsions, opisthotonos, gradual failure of respiration and circulation, coma and death. When the animal lives longer after small intravenous injections, or after subcutaneous injection, there develops a characteristic symptomatology of salivation, marked diarrhea, and fall of temperature, with marked anorexia, emaciation and depression. With subcutaneous injection of .015 to .06 c.c., death usually takes place from the fourth to the tenth day.

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The specific microscopic pathology of the local lesions of dichlorethylsulphide poisoning consists in degeneration and necrosis of the cells with which it comes in contact. The earliest microscopic change is pyknosis of the nucleus and cell body, followed by hydropic degeneration, liquefaction or coagulation necrosis. In the skin, hyperemia, with regeneration of the damaged cells, pigmentation, vesicle formation, desquamation of the dead epidermis or eschar formation mark varying stages of severity of the lesion. The degenerative changes extend deepest in the hair follicles and sweat glands. In mild burns without vesication the papillary layer of the corium may show a greater degree of necrosis than the epidermis itself, thus explaining the frequent occurrence of Nikolsky's sign. Large pigmented chromatophores may be the only living cells left in the papillary layer. In severe burns the necrosis may extend entirely through the corium. In the cornea, pyknosis and simple or coagulation necrosis of the corneal epithelium and interstitial substance, even to the endothelial layer, in extent varying with the degree of