CLINICAL AND BIOCHEMICAL ANALYSIS OF HEPATOTOXIC EFFECT OF TRINIROTOLUENE

A thesis

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BY

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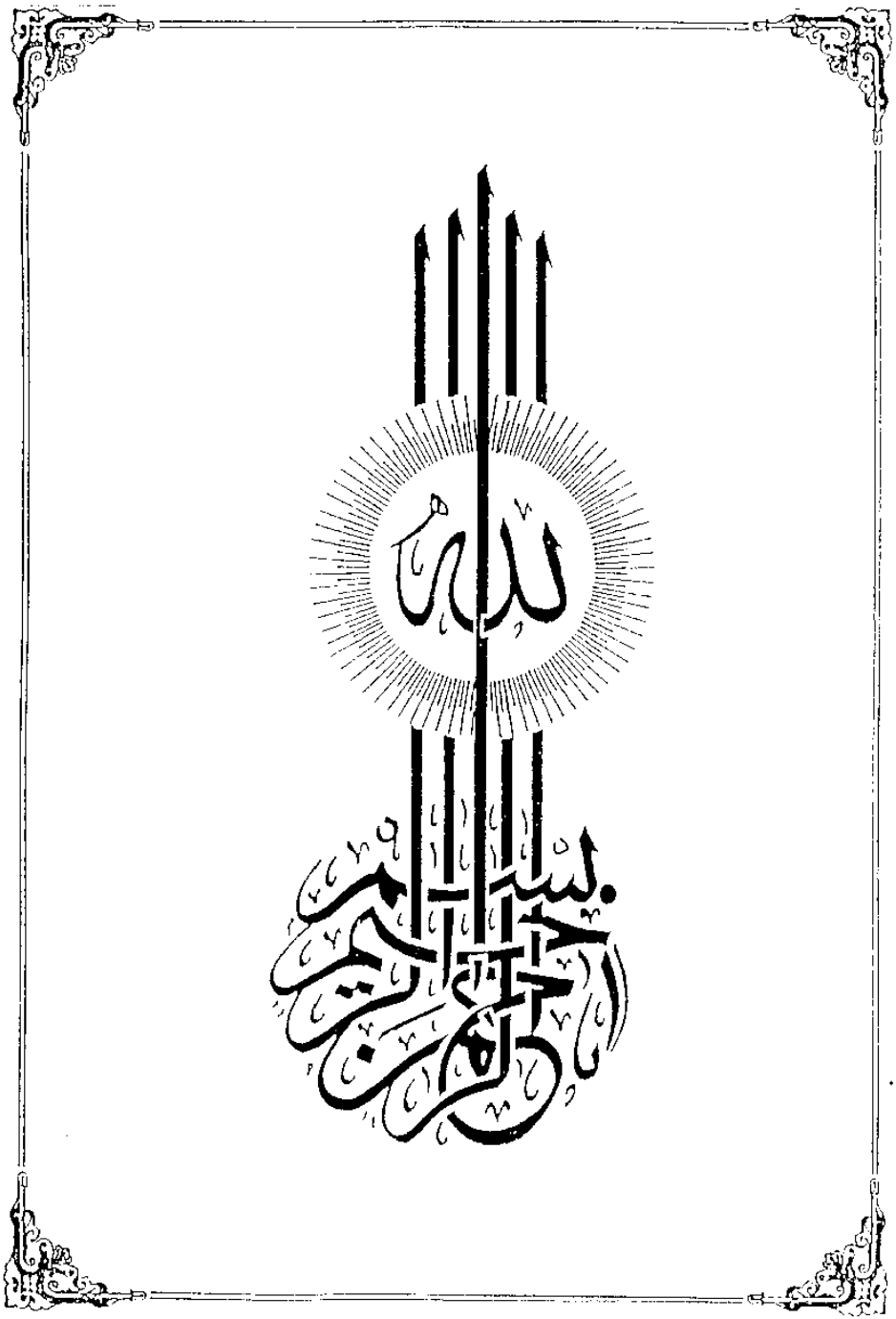
" The Candidate"



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INTRODUCTION

Trinitrotoluene or alpha TNT is a pale yellow crystalline solid material which was discovered in the ninteenth century, but its explosive properties became known later, when it was introduced into large-scale used during World War I and became the standard explosive in the World War II (Davis 1941) .

TNT is produced by full nitration of toluene by mixture of sulphuric and nitric acidsin a multistage process in which the temperature is gradually raised to about 100^{o}C to produce TNT .

Absorption of TNT takes place mainly through the skin, but also inhalation and ingestion can not be ignored (Hunter 1979). meanwhile the excretion of its metabolite occurs through the urine (Webster 1916) .

The toxic effects of TNT are numerous which can be summarized as, cyanosis (anilism). Through methaemoglobinaemia, toxic jaundice, toxic anaemia of aplastic type, gastritis with dyspepsia and dermatitis (Tyrer and Lee 1979).

Cardiovascular changes have been described as well by few authors(Master and Friedman 1942: and Soboleva 1969).

Sub-endocardial ischemic changes which are rather permanent and not transient (Emara and El-Samra et al 1981).

The aim of this study is to express a suitable screening test as an evidence of TNT exposure and also a simple, easy and practical test, indicating early intoxication, moreover to evaluate the hepatotoxic effect of TNT in the circumstances of our military industry.

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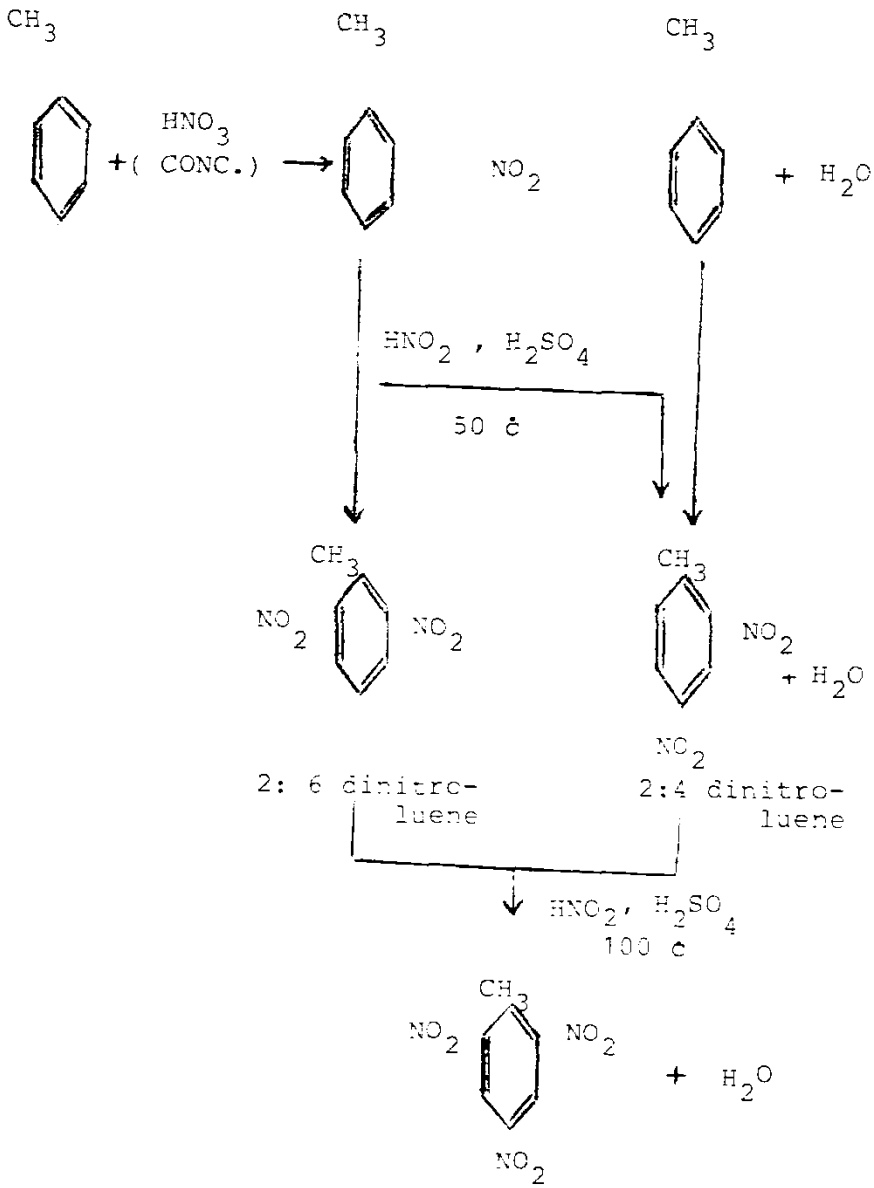
REVIEW OF LITERATURE

Trinitrotoluene (TNT) was discovered by Wilbrand in 1863, but its explosive properties became known later when detonators were adopted as means of setting high explosives. It was introduced into large-scale use during world War I and became the standard explosive in World War II (Davis 1941) . 2, 4, 6, trinitrotoluene which has the molecular formula $CH_3C_6H_2(NO_2)_3$, is prepared by nitration of toluene $C_6H_5\text{-}cH_3$, which is obtained by distillation of Coal tar or of crude petroleum, and is made synthetically from other components of petroleum. The nitration is usually carried out in three stages, the first yielding mononitrotoluene, the second, dinitrotoluene and the third TNT (Marshall 1932).

The chemical process can be summarised as follow: Mixed nitric - sulphuric acids are used for the nitration, the strength increasing from stage to stage . In the course of this preparation isomers of the desired product-alpha TNT ." 2,4,6 trinitrotoluene" are formed in small quantities. Since these are less stable to heat and have the tendency to form low melting mixtures, and hence cause exudation from loaded munitions, they are removed to purification is best accomplished by the washing of crude TNT with 5% Sodium sulfite solution (Davis 1941).



2,4,6, Trinitrotoluene

2,4,6 trinitrotoluene or alpha TNT is a pale yellow crystalline solid, commercial TNT is handled in blocks from which an objectionable oily exudation arises as a result of impurities , including small amounts of other trinitrotoluene and traces of dinitrotoluene (Hunter 1975).

Alpha TNT has a molecular weight of about 227.13, specific gravity 1.65, melting point 80.35, boiling point 240°c, Vapour pressure 0.046 mm Hg (82°C). Acute fatal dose is estimated to be 1-2 g. and TLV in air is 1.5 mg / m^3 (Dreishbach 1977).

Alpha TNT is readily soluble in ethyl ether, acetone, benzene, toluene, chloroform, carbon tetrachloride, and insoluble in water.

Other isomers of TNT, namely 2,3,4 TNT B $C_6H_2CH_3(NO_2)_3$.
2,4,5 TNT (Y) $C_6H_2CH_3(NC_2)_3$
2,3,5T,TNT (E) $C_6H_2CH_3(NO_2)_3$ and
3,4,5 TNT $C_6H_2CH_3(NO_2)_3$ (Devereux 1955).

Uses of TNT:

The wide adoption of TNT as an explosive is indicated by its many synonyms, which include such names as trilit, trinol, tritolo, triton , trolite, trolyl, its main use is as a brusting charge in shells, bombs and mines. Owing to its very marked deficiency in oxygen it is more often used mixed with substance rich in oxygen; amatol and ammonal contain ammonium nitrate, and baratol contain barium nitrate (Hunter 1975).

Metabolism of TNT :-

The main route of absorption of TNT is through the skin , but of course , ingestion of the substance and absorption through the respiratory tract of dust and fume can not be ignored (Hunter 1975) .

Legge (1917) satisfied himself by studies of the precise occupation of workers with toxic jaundice that the skin had been the route of absorption of TNT .

Moore (1918) investigated the problem of skin absorption of TNT by experiment upon himself, after showing that

the Webster test of his urine was negative; this test was discovered by Webster (1916) and later improved by Ingham (1941). The principle of this test depends on extraction of the metabolite of TNT in the urine by ether, the intensity of colour developed after addition of alcoholic solution of potassium hydroxide, indicate qualitatively the amount of the metabolite in the urine; Moore went into an orchard attached to a factory and rubbed into the palms of his hands intermittently for about six hours an amatol pellet containing 20% TNT. He was careful to refrain from going near any part of the factory where there was TNT dust or fume. After two hours a specimen of urine was passed and this showed a positive Webster test. This reaction went on increasing until next day when its intensity was about the same as that given by the urine of the shop- workers.

The tint remained and gradually increased for a period of ten days, although he neigther rubbed TNT in again nor went near any source of dust or fume . The first morning after rubbing in the amatol (TNT and ammonium nitrate) , he wake with all the symptoms of a minor attack of TNT illness, he had marked fron-

tal headache, with a feeling of nausea and intermittant abdominal pain, this abated shortly, but a feeling of malaise and drawsiness persisted for about two days , After a fortnight, and when his urine had become free from TNT metabolite, he repeated the experiment with the same result as before.

Absorption of TNT is greater in hot wheather, not only because the worker exposes his arms and neck to a greater extent, but also because sweat helps to dissolve the TNT dust on the skin so hasting its absorption . Because TNT is absorbed through the skin, amatol is more productive of poisoning than TNT alone. Ammonium nitrate is hygroscopic and keeps the skin of hands and forearms moist., thus dissolving TNT (Hamilton and Johnstone 1945) .

On the other hand the presence on the skin of oil and grease, in which TNT is soluble enhances absorption and increases the chances of intoxication, it is generally stated that inhalation of the fumes is without danger, but this view is not shared by some authors (Schiff 1966), but he shared others in the skin absorption of TNT as a major route and the mucous membrane to a lesser extent.

The fate of TNT in the body has been studied but with little result. Webster (1916) devised a test for derivative of TNT namely 2,6 dinitro-4- hydroxylamino-toluene- which is excreted in the urine. Webster and others have since improved the test,making it sensitive to 1 part in 10.000 (Ingham 1941). The urine of practically all workers in TNT contains the substance identified by Webster, but in some there is only a minute trace, in others an intense reaction, and there may be a considerable reaction where there is no sign of TNT illness or illness with only a moderate degree of reaction (Hunter 1975). " This observation was not explained by the author" .

By a simple modification of Webster test the sensitivity increased and a positive result are more frequently obtained, the most simple principle of this test depends on boiling a mixture of urine and sulphuric acid before adding the ether, thereby ensuring a good extraction of TNT product from the urine, the test is further improved and the chances of detection increased still more by using four times the quantity of urine recommended by Webster (1941) .

It is well known that the follow up of TNT after its entery into the body systems, is so difficult, this is because TNT like many other toxic substances becomes conjugated

in the body in a reaction which changes it and rendering it less poisonous. Moreover once TNT has passed into the body it can not be longer taken up by its well known solvents , and must be firstly set free before it can be recognised by chemical tests, so a sample of urine from A TNT worker loaded up with altered TNT product can not be extracted unless treated first by acid, to let TNT product free and so can be discovered in the extractive. It is easy for the observer dealing with this test to develop after a little experience in using the test an arbitarory scale of intensity which will enable him to judge the degree and follow relative intensities in the urine (Ingham 1941).

In the manner described before a fairly good rough standard of intensity can be obtained serviceable for clinical work and experimental observation, when there is doubt as to the presence of the early diagnostic symptoms, then the test should be made, and if it gives a fairly high result the worker should at once be taken of work in TNT and the urinary test made if possible daily in succeeding two or three days (Ingham 1941).

Symptomatology and clinical manifestation of TNT poisoning:-

The clinical manifestation of TNT poisoning include dermatitis, cyanosis, gastritis, toxic jaundice and anaemia, the hands and sometimes the face and hair are stained orange with TNT causing an appearance easily distinguishable from jaundice (Hunter 1975). Dermatitis arises on the parts exposed, as the hands, forearms, legs, wrists and ankles, it begins between the fingers and on the thenar eminence as a pink papular eruption on an erythematous background, as it spreads over the wrist and forearms, the papules become confluent, desquamation is the rule, and if it is severe it may lead to exfoliation, the irritation is so intense that removal from contact is essential (Hunter 1975). These signs and symptoms arise from contact and not from inhalation.

The onset of the symptoms is usually insidious, with anorexia, nausea and vomiting, Jaundice appears within two weeks and often is followed by hepatomegaly (Stewart 1919). in severe cases, abdominal pain is a prominent feature , and the liver may be small, the course tends to be prolonged and often is complicated by the development of ascites and haemorrhagic phenomena. Occasionally there is an associated