stances—e.g., ammonium nitrate (amatol), barium nitrate (baratol). It is a highly toxic substance, of which the clinical manifestations are as follows:

1. The hands and, more rarely, the face and the hair are stained orange, but the staining is not so deep as with C.E. This staining should not be confused with the yellowish coloration due to jaundice.

2. *Dermatitis*.—This arises on those skin surfaces which are exposed to direct contact with the explosive—i.e., hands, forearms, neck, wrists, and ankles, the last three areas through friction from the operator's clothing. It seldom appears on the face, but this may be involved in a general outbreak all over the body. On the hands it starts as a sago-grain eruption, and is particularly evident between the fingers and on the thenar eminence. Elsewhere it takes the form of a coalescing papular eruption with areas of erythema. Desquamation is the rule, and may be severe, leading to complete exfoliation of the hands and feet. Small "powder"-holes are also seen. The irritation is intense; and treatment is the same as for C.E. dermatitis—i.e., removal from contact and local application of bland lotions and ointments. One attack of T.N.T. dermatitis, unless unusually severe, is no bar to further employment with the explosive.

3. *Cyanosis*.—T.N.T. exerts a specific action on the haemoglobin, forming a mixture of methaemoglobin and NO-haemoglobin. A large percentage of these workers are "cyanosed" to a greater or lesser degree and present a typical appearance. The lips, tongue, and mucous membranes become a greyish-mauve shade, very different from the true cyanosis of cardiac or lung disease. There is no real anaemia, and very often the condition is symptomless. In fact, we have met workers looking quite purple who declare that they have never felt better in their lives. When present the symptoms are those of oxygen dearth—i.e., fatigue, lassitude, and dyspnoea on exertion. At one time it was our practice to remove from T.N.T. contact all workers showing this sign no matter to what degree, but now we allow mild cases, in which the patients are otherwise well, to remain in contact under observation.

4. *Toxic Gastritis*.—This is a definite syndrome, and is not to be confused with other forms of gastritis arising in T.N.T. workers, including latent hypochlorhydria, which may be unmasked by the action of the trinitrotoluene. The symptoms are: (1) central epigastric pain of a colicky nature, relieved by rest but not by vomiting, and bearing no relation to food; (2) nausea with or without vomiting; (3) a feeling of tightness in the chest; (4) anorexia; and (5) constipation. The cardinal symptom is pain. These patients present a distinct appearance. Cyanosis may or may not be present, but they show a greyness of the face, with a worried expression, and often a definite pallor over the bridge of the nose extending on to the cheeks; the tongue is usually clean. Examination of the abdomen reveals nothing except slight epigastric tenderness, probably due to the constant retching and vomiting. The treatment again is immediate removal from all contact, including the changing of any contaminated clothing and a thorough cleansing of the skin. In very early cases the patient need not be suspended from work, but if there is much vomiting—in our opinion the most important symptom—rest in bed is indicated, combined with saline purges and a high carbohydrate diet containing plenty of fresh fruit and vegetables. There is some evidence to show that vitamin C in large doses may be of value in these cases. Workers who have had a severe attack of toxic gastritis should not be allowed to return to T.N.T. work.

5. *Toxic Jaundice*.—Fortunately this is a rare complication, but it carries a 30% mortality, and all such cases must be treated as serious. It may be heralded by an attack of cyanosis or toxic gastritis, or it may arise *de novo*, patients being found who are symptomless and maintain that they feel perfectly well. The jaundice starts in the conjunctivae and spreads rapidly to the skin. It is a late and grave sign, and indicates severe liver damage. These patients should always be removed to hospital, as it is impossible to carry out adequate treatment at home. The treatment is the same as that for toxic jaundice due to other causes. On admission to hospital the patient should be given a warm bath, and if possible the skin should be scrubbed with acetone or ether to remove any trace of T.N.T. that may still be present.

Special attention should be paid to the hands, nails, and hair. Cyanosis may be treated with inhalation of oxygen and carbon dioxide, but this is only necessary where there are definite symptoms of oxygen dearth. The bowels should be kept open by saline purges, and the diet should contain fresh fruit and vegetables, and be rich in carbohydrate, calcium, and vitamin C. It has been maintained that Webster's urinary test for T.N.T. is invariably negative in cases of toxic jaundice, but we are of the opinion that this is not so. We have obtained a positive reaction in a severe case six weeks after admission to hospital. Prognosis on these cases is difficult and should be given with great caution until the patient is well on the way to recovery and the jaundice has cleared up. It is often months before they are fit to return to work, and on no account should any patient ever be allowed back on T.N.T.

6. *Aplastic Anaemia*.—This is a still rarer complication, nearly always fatal and sometimes preceded by jaundice. We have seen three cases, all of them fatal, but in only one was there a definite history of jaundice.

Conclusion

These manifestations appear formidable on paper, but the percentage of workers in contact who are affected is small. Our experience points to the fact that, other things being equal, personal idiosyncrasy must play an important part in the production of toxic symptoms. We are sure that factory medical officers as a body would willingly co-operate with general practitioners in helping to diagnose these somewhat unusual conditions.

Medical Memoranda

Preliminary Note on the Properties of s-Methyl Isothiourea Sulphate

While working with some thiourea derivatives it was observed that s-methyl isothiourea sulphate when administered intravenously in animals raised blood pressure and stimulated respiration. Further observations showed that it also acts when given by mouth. The pharmacological properties of the substance have apparently not been described hitherto, and are manifest in doses which after repeated trials appear to be harmless in lower animals and in man. The circulatory effects have been observed in the dog, cat, rabbit, and man. The rise of blood pressure is either mainly or entirely of peripheral origin, since it takes place after destruction of the central nervous system. The blood-pressure increase is not likely to be the result of stimulation of sympathetic-nerve endings, as it occurs when these endings are paralysed by ergotamine.

Other smooth muscle besides that of the blood vessels is contracted by s-methyl isothiourea sulphate, notably plain muscle of the isolated intestine. In the whole animal, however, this action on the intestine is not a prominent feature except with big doses. A more detailed communication describing the action in animals will be published shortly, in collaboration with Dr. M. McGeorge (Dunedin) and Prof. Mahomed Sherif (Cairo).

Following animal investigations it was decided to study the action in man. The work in this connexion began in collaboration with Dr. Nassif in Cairo and has been continued by me. It has been shown in healthy men that doses of 0.2 to 0.4 gramme of s-methyl isothiourea sulphate when taken orally cause slowing of the heart and usually a blood-pressure rise. No subjective sensations have been observed to accompany these changes. Two doses of 0.4 gramme given with an interval of about thirty minutes between them have been administered on a number of occasions without leading to subjective sensations. The fall in heart rate is then as much as 20 beats per minute, and in some instances the heart rate has dropped to below 50. On several occasions healthy volunteers carried out a standard Army exercise-tolerance test before and after administration of

s-methyl isothiurea sulphate and observed no special difference as a consequence of taking the substance.

ITS POSSIBLE VALUE IN CASES OF SHOCK

Some observations have been made by me in man and in experimental animals to ascertain if this substance might be of value in the treatment of surgical shock. It has been noted in about twenty obviously moribund patients, mostly medical cases with terminal circulatory collapse, that the systolic blood pressure may rise promptly from, say, 60 to 120 mm. after the intravenous administration of 0.2 to 0.4 gramme. The diastolic pressure is raised proportionally. The blood pressure remains elevated for fifteen minutes to one hour. The heart rate, however, may fail to slow or does not diminish to the degree observed in health. Some of these results were encouraging in that several moribund patients made a temporary recovery. Two cases of severe surgical shock were treated by the intravenous injection of s-methyl isothiurea sulphate. Both patients survived, and improvement coincided with the administration of the substance. It is regretted that most of the clinical observations were not made on cases of surgical shock, but opportunities for a satisfactory study of this subject are lacking in New Zealand.

More definite evidence has been obtained that the substance is of value in treating acute shock produced experimentally in healthy animals. Thus crushing of limbs and extensive abdominal injuries were employed in anaesthetized cats and dogs to reduce the level of the blood pressure to 30 or even 20 mm. Hg. Ordinarily when the blood pressure has been reduced to such levels cessation of the heart beat usually follows within a minute or two. A majority of animals with blood pressures of 20 or 30 mm. Hg were revived for periods of one or more hours when treated with s-methyl isothiurea sulphate intravenously. It seems, therefore, that the substance delays death if given to animals in extreme traumatic shock. There is thus a chance that the substance would be useful to tide over air-raid casualties which cannot be removed to a place with facilities for transfusion.

The substance also may be worthy of clinical trial in those cases of traumatic shock in which a vasoconstrictor substance could be of value, but even so it should be regarded as an adjuvant and not as an alternative to methods of treatment which restore the blood volume. Patients whose blood pressures remain at a low level despite restoration of the blood volume might be benefited by s-methyl isothiurea sulphate.

In my patients dosage has been controlled by observing the pulse and blood pressure. It appears that in divided doses as much as 1 to 1.5 grammes may be administered in the course of three hours, and probably more would be tolerated. Solutions have been sterilized by tyndallization and kept in ampoules, 0.2 gramme in 2 c.cm. So far only one contraindication to the use of this substance has been found—namely, that it should not be employed in congestive heart failure.

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Malachite in the Control of Bilharzia

The possibility of controlling bilharzia in Southern Rhodesia has been under investigation for the past two years. This work was begun at the instigation of the medical director of Southern Rhodesia, Dr. A. P. Martin, with the aid of a grant from the trustees of the State lottery. I proceeded to the colony in the first place in company with Sir Malcolm Watson, director of the Ross Institute of Tropical Hygiene. Certain results of this work seem to be important enough to merit immediate announcement.

An essential phase of the investigation has been a search for effective and practical means of destroying the intermediary hosts of human bilharzia—namely, the snails *Physopsis globosa* and *Biomphalaria pfeifferi*. Previous attempts to destroy these dangerous snails have centred largely around the use of copper sulphate. The principal objections to the use of this substance are its relative toxicity to man and other mammals, its great solubility (approximately ten parts of copper per hundred), and its high cost. Copper carbonate is at least as lethal to snails as is copper sulphate, it is much less soluble than the sulphate (approximately one part of copper per million), and in saturated

solution it has been proved by experiment in Southern Rhodesia to be non-toxic to white rats when given in repeated doses. The relatively high cost of copper carbonate as well as of the sulphate has led to a search for some less expensive form that would be suitable for control work on a large scale.

Malachite (mineralized basic copper carbonate) when ground fine enough to pass through a 200-mesh sieve has been found to be suitable for this purpose. In this condition malachite from two sources in Southern Rhodesia has been proved to be effective in destroying snails both in the laboratory and in actual bilharzial pools in the field. The present cost of malachite in many parts of Africa is less than £1 a ton. Finely powdered malachite yields an effective concentration (dissolved and colloidal) of 0.5 part of copper per million when placed in natural water (from the Macabuzi River, near Salisbury, S.R.). It has been found that the solubility of this substance is considerably increased by mixing it with fresh brewer's waste (i.e., fermented barley) or with the powdered pods of a common Rhodesian tree, *Swartzia madagascariensis*.

These methods of destroying snails will play an important part in a campaign for the control of bilharzia in Southern Rhodesia which will begin shortly. A full account of the control methods to be used is in preparation.

I am grateful to the Medical Director of Southern Rhodesia for permission to publish this note.

Salisbury, Southern Rhodesia.

ALAN MOZLEY, D.Sc Ed.

Melanotic Carcinoma: Sudden Spread after Hysterectomy

The following case may be interesting enough to be worth recording.

CASE REPORT

The patient, aged 41, had hysterectomy performed for fibroids of the uterus on April 25, 1941. Her only complaint was menorrhagia. At operation a routine inspection of the abdominal contents revealed no other abnormality. Pre- and post-operative examination of the chest showed no disease, and the patient left hospital after a normal convalescence. The pathological report on the uterus indicated simple myoma only.

The patient was readmitted on August 1 complaining of abdominal swelling and vomiting for two weeks; for one week she had been breathless. Symptoms had come on quite suddenly twelve weeks after operation. On admission she was cyanosed and breathless at rest; there were scattered subcutaneous black nodules, including three in the abdominal scar; the abdomen was distended with fluid, but a large nodular liver was readily palpated. Search for a primary melanoma revealed only a small scar over the left clavicle. The patient then gave a history that five years ago she had had a "black naevus" there. It was treated with carbon dioxide snow, but increased in size—whereupon it was excised under local anaesthesia. There had been no recurrence since.

She died on August 7. At necropsy melanotic carcinomatous deposits were found in almost every organ of the body—heart, thyroid, lungs, meninges, and brain. The liver weighed 110 oz., and there were profuse deposits in the mesentery, kidneys, spleen, suprarenals, pancreas, and stomach. The abdominal scar was studded with melanotic deposits. The urine gave a positive test for melanogen.

Twelve weeks previously there had been no macroscopical abdominal deposits. If the sudden spread of melanotic deposits was purely coincidental the rapid dissemination after five years' complete quiescence is noteworthy. It is, however, interesting to speculate whether the operation on a distant site initiated the spread; whether, in fact, the malignant cells had lain dormant for five years only to be stirred into activity by the mechanical or physiological disturbance of the operation. Although so far as I know no mechanism for this is described, it seems to be a more possible explanation.

My thanks are due to Mr. Edgar Freshman, under whom the case was admitted, for permission to report it, and to Dr. Norman Ashton, who carried out the necropsy, for the use of his report.

Kent and Canterbury Hospital.

LESLIE J. TEMPLE, F.R.C.S.