Discussion

How can the marked difference in size of the elementary bodies as determined by filtration experiments and microscopical methods be explained? It should be remembered that the size of the virus particles as measured by means of collodion filters represents the size of the *smallest* of the living bodies and not that of the average of the stained elementary bodies. Have fixation and staining any effect on the size of the particles? The answer to this is strikingly in the affirmative, and to a much greater extent than most of us realize. In 1929 I stained a film containing *Treponema pallidum* in Giemsa for fifteen to twenty minutes, and after washing and drying examined it with the 8-mm. or 1/3-inch apo-objective by dry dark-ground illumination, without any cover-glass or mounting medium. A spirochaete was very easily found by this means, partly because the eosin red of the Giemsa shows up brilliantly by dark-ground illumination, but chiefly because the difference in its refractive index and that of air is so great. The position of the spirochaete was logged, and ringed with the marker. The oil-immersion objective was then turned on, and the spirochaete was practically invisible; only after prolonged careful search was it seen, and it appeared as the very thinnest and finest spirochaete possible. The slide was placed back in the stain for twenty-four hours, and then it was markedly thicker and very easily seen with the oil objective. A film or a section stained by any of the flagella stains after mordanting, or in silver-impregnated preparations, shows spirochaetes and leptospira as very thick coarse structures, easily seen with quite low-powered objectives.

As the virus bodies are probably very minute organisms, why should the difficulty of examining them be further increased by restricting the examination to them in the living condition? Do we examine sputum for tubercle bacilli, or the diphtheritic membrane or its cultures for the bacilli, in the living unstained preparations? The size of all bacteria is determined in stained preparations, and in the case of the tubercle bacillus in films mordanted by carbolic acid and heat. The size of the tubercle bacillus is generally given as varying from 2.5 to 3.5 μ in length and 0.3 μ in thickness: has anyone detected this bacillus in its unstained living condition, and can anyone even guess at its size in its living state?

The only reason I can imagine why the elementary bodies are studied in their living unstained state is that the very few exponents of ultra-microscopy would have us believe that this is the only correct method: even if this method were adopted the viruses would never be seen but could only be photographed.

Conclusions

I am of the considered opinion (a) that all the filterable virus bodies, including the smallest and the so-called invisible virus of foot-and-mouth disease and that of infantile paralysis, are easily within the range of the ordinary microscope when used correctly; (b) that ultra-microscopical methods are not essential, and their use has so far added little to our knowledge.

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CLINICAL MANIFESTATIONS OF TETRYL AND TRINITROTOLUENE

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Since many filling factories have been built recently in different parts of the country it might be of interest to practitioners to know something about the effects on the human body of continued exposure to tetryl and trinitrotoluene.

Tetryl, or "C.E."

This compound is a sharp crystalline powder, yellow in colour. Its clinical manifestations are as follows:

1. The powder stains the skin of the hands, face, neck, and also the hair, and this colour deepens to orange on exposure to sunlight. It should be emphasized that the staining varies considerably in different workers and bears no relation whatever to any of the following manifestations.
2. New workers sometimes complain of a sharp tingling sensation in the nose. This causes sneezing and more rarely epistaxis, and is due to the irritating effect of the crystals on the nasal mucous membrane.
3. The commonest complaint from tetryl workers is dermatitis. This starts as an erythema, followed by a papular eruption accompanied by some exfoliation. It arises in the region of the sweat glands of the face—i.e., the naso-labial fold and submandibular regions of the neck. It may spread all over the face, causing severe irritation, and in some cases gross oedema of the eyelids, which may prevent the patient opening the eyes for two or three days. In severe cases secondary sensitization may occur on the hands, arms, and trunk. Should tetryl come into contact with the conjunctivae a mild conjunctivitis results. Constitutional symptoms are present only in the more severe cases, usually as headaches and general malaise. They are to some extent understandable, as patients suffering from extensive rash often lose sleep. The treatment of C.E. dermatitis is first and foremost removal from contact with the powder. It is not enough merely to change the worker's occupation; he or she must be removed right away from the vicinity of the powder, otherwise the condition will be aggravated by the small amount of dust present in the atmosphere in all shops where tetryl processes are carried on. It is also important that the worker be given a complete change of working clothes. The local treatment, generally successful, consists in frequent applications of calamine lotion or, if there is much desquamation and drying of the skin, lotio calaminae oleosum. A word of warning is, however, necessary when using the latter preparation: tetryl workers should be told on no account to use oily preparations on their skin as a preventive measure, as by so doing ideal conditions are produced for the development of a second attack of C.E. dermatitis. Mild cases clear up in a few days, but severe rashes often persist for two or three weeks. Suspension from work is seldom necessary. When the dermatitis has quite cleared up the worker may return to contact work, but if a second or third attack occurs it is an indication that the patient is very susceptible and should be removed permanently from tetryl work. In our experience those workers who develop oedema of the face and periorbital tissues are bad risks, and we remove them permanently from contact at the first outbreak of the rash.
4. Although it is not generally admitted that tetryl gives rise to any constitutional symptoms, we have found that numbers of new workers complain of epigastric pain, with nausea or vomiting. These symptoms, like those of T.N.T. toxic gastritis, bear no relation to food and are seldom severe enough to keep the patients away from work. Such workers are removed from contact until the symptoms abate. They are then allowed to return, and usually no further trouble arises.

Trinitrotoluene, or T.N.T.

T.N.T. is a yellowish crystalline powder more stable than C.E. and is used either by itself or mixed with other sub-

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