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APLASTIC ANAEMIA DUE TO TRINITROTOLUENE INTOXICATION

BY

M. A. DOBBIN CRAWFORD, M.D., F.R.C.S.I.

Assistant to the Chief Medical Officer, Ministry of Supply

Trinitrotoluene (T.N.T.) is the most generally used of all chemical war explosives. Used alone, or mixed with other compounds, it forms the bursting charge in shells, mines, and bombs. The filling of these weapons of war is still largely done by hand, with the use of tools made of wood or non-ferrous metal. A main pre-occupation of the medical officer in an explosives filling factory is the protection of the workers from absorption of T.N.T. Unfortunately, this material finds ready entrance to the body, whether in the form of fume or dust, mainly by inhalation, but also by ingestion and through the skin. When the dose is small and the body healthy, T.N.T. is rapidly detoxified in the liver, the metabolic products are excreted mainly by the kidneys, and no appreciable harm is done. When, however, the dose is larger, or for some reason the detoxifying mechanism in the body is unable to cope completely with the invasion, then T.N.T. or, more probably, the early and even more poisonous products of its metabolism (Channon *et al.*, 1944) accumulate and circulate in the blood stream, inflicting damage upon susceptible tissues.

The clinical manifestations of T.N.T. intoxication are six in number: cyanosis, dermatitis, anilism, toxic jaundice, toxic anaemia, and toxic purpura, roughly in this order of frequency. Each may appear separately from the rest, or in varying combination, simultaneously, or in processional order. The only exception is T.N.T. dermatitis, which rarely, if ever, is present in conjunction with the more serious developments. This paper puts on record all the cases of toxic anaemia and toxic purpura due to T.N.T. which occurred in the United Kingdom, and were noted, during the 1939-45 war.

Toxic anaemia was first made notifiable in January, 1942. Some 15 cases, all ending fatally, were recorded

during the first world war, and the majority are noted in the *Proceedings of the Royal Society of Medicine*, 1917, Vol. X, where a symposium on the effects of T.N.T. is reported. Further comments may be found in the Medical Research Council Memorandum, Special Report Series No. 58, 1921.

During 1939 no toxic anaemia was noted amongst T.N.T. workers in the United Kingdom. In 1940 there was 1 case, which recovered; in 1941 there were 8 cases, with 6 deaths; in 1942, 9 cases, with 3 deaths; in 1943, 4 cases, with 3 deaths; in 1944, 3 cases, with 2 deaths; in 1945, 1 case, which recovered; in 1946, 1 fatal case. A total of 27 cases and 15 deaths.

Of these 27 cases 3 were atypical, mild in degree (early?), but the remaining 24 were all diagnosed as aplastic anaemia due to T.N.T.—9 of these persons recovered and 15 died.

Effects of T.N.T. Upon the Blood and Bone Marrow

The assimilation of T.N.T. results in a variable degree of anoxaemia. There may be a haemolysis of some of the red cells circulating in the blood stream; in other erythrocytes the haemoglobin may be destroyed in the cell; others are

be most carefully watched, for it must be remembered that reticulocytosis has been found to increase greatly after workers have been removed from contact (Stewart *et al.*, 1945).

With further intoxication, the blood-forming tissues begin to fail, the marrow itself becomes hypocellular, and the cells in the blood are reduced in number. "There is a profound normocytic anaemia with agranulocytosis and a low platelet count. All the blood-forming elements are affected" (Lane, 1942). The casualties cannot be replaced, and a progressive aplastic anaemia develops, which in three of every four cases known in the United Kingdom has ended fatally. The hazards of such an aplastic anaemia are very great. Although by sufficient and repeated blood transfusions the patient may be kept alive, there is no certain favourable prognosis until the blood-forming function of the marrow has been actively restored. During the months or years which may elapse before recovery is fully attained, prognosis must be guarded—a crop of boils, a septic tooth, an acute infection of the tonsils, an attack of influenza, or even perhaps an injudicious dose of sulphonamide may at any moment bring catastrophe.

It has been said that all elements of the blood are affected, but the degree to which each type of cell suffers is very variable. It is rare to find that the white cells are only little affected when the red cells are depleted. In many cases a neutropenia is the most marked effect, proceeding to agranulocytosis, while in others it is chiefly the platelets which have suffered loss—a low platelet count with increased fragility of the capillaries becomes established, and the condition is one of toxic purpura.

Deterioration is rapid, particularly when the anaemia is associated with a thrombocytopenic purpura. In these cases the decline is lamentably swift.

Toxic purpura has been associated with aplastic anaemia in the most severe intoxications. A purpuric eruption has also been noted at necropsy in the majority of deaths from toxic jaundice due to T.N.T.

The low incidence of intoxication amongst the thousands of workers exposed to T.N.T. was undoubtedly due to careful pre-employment examination, the unfit being rejected, and to the precautions taken to prevent any undue absorption of the fume or powder. It is clear that in healthy individuals, constantly exposed to a not excessive dose of T.N.T., a tolerance can be developed: detoxification is adequate, the marrow responds to the call for an extra supply of cells to the blood, and a serviceable equilibrium is

FIG. 1.—Haemoglobin percentage of T.N.T. workers and controls in a Royal Ordnance factory, 1944. (Haemoglobin estimation by Haldane and Sahli.)

temporarily deprived of their oxygen-carrying capacity by the formation of methaemoglobin, and yet others suffer a permanent fixation of their pigment in the form of sulphaemoglobin (Joep, 1946).

A slight degree of anaemia may persist for some weeks or months while the bone marrow maintains its capacity to restore the blood cells to their normal strength when absorption of T.N.T. has ceased. A decrease of 10% in the haemoglobin commonly occurs, but any further diminution calls for investigation (Ramsay, 1946) (Fig. 1).

At the same time, however, the marrow is affected by the circulating poison. The first reaction is a stimulation of the haemopoietic tissues: the bone marrow becomes hyperplastic, and to a surprising degree—the shaft of the femur and the ribs and vertebrae have all been found filled with active red marrow. There is an increase in the number of reticulocytes circulating in the blood stream, and a moderate leucocytosis; the monocytes may be increased in number (Hamilton, 1946). A slight increase in the size of the red cells may be observed. The reticulocytes were estimated in 184 workers exposed to T.N.T. (Ramsay, 1946). In 20% of these there were more than two reticulocytes per 100 red cells; these counts are probably associated with some hyperplasia of the marrow, and such workers should

FIG. 2.—Average haemoglobin percentage of workers in T.N.T. for varying periods in a Royal Ordnance factory, 1944. (Haemoglobin estimation by Haldane and Sahli.)

established. This was confirmed by the late Helen Ramsay when, in 1944, she determined the haemoglobin percentage in 785 workers in contact with T.N.T. and in 242 controls who were not exposed to this compound. In four of the five groups examined the haemoglobin percentage was higher in those who had been exposed for over a year than in those who had worked in contact for 6-12 months (Fig. 2).

Condition of the Blood in 27 Cases

The blood picture produced by the impact of T.N.T. was aggravated in many of these cases by the resulting haemorrhages. Haemorrhages were noted clinically in 11 of the fatal cases and in three of those who recovered. Haemorrhages were found after death in three other cases (in two of these clinical records are not obtainable). Bleeding from the gums and from the nose occurred most frequently; there were retinal haemorrhages in three cases, conjunctival haemorrhages in two others. Menorrhagia occurred in two cases, and in one other there was uterine haemorrhage so severe that it led to a mistaken diagnosis of abortion and the uterus was explored and emptied—of blood clot only. Such an error occurred in two cases during the first world war (O'Donovan, 1921).

Red Blood Cells

Number.—The counts recorded were: 630,000 per c.mm., the lowest count, in a fatal case; 730,000, the lowest count recorded with recovery; 1,000,000 or fewer in 7 cases; 1,500,000 or fewer in 18 cases; 3,000,000 or fewer in 23 of the aplastic anaemia cases (no record in one case). The three milder cases of toxic anaemia were found to have their red cells reduced to: 3,380,000, 2,790,000, and 3,504,000 per c.mm.

Size.—The anaemia was normocytic or macrocytic. Anisocytosis was recorded in 14 cases; in 12 of these, red cells larger than normal were seen (taking the normal mean corpuscular diameter as from 6.6 to 7.7 μ). Eight cases showed macrocytes of diameter up to 8.4 μ , two of them showing megalocytes up to 10 μ in diameter; of these two cases, one recovered, while in the other a terminal examination before death found red cells of 12.5 μ and even 15 μ in diameter. In both, occasional microcytes, diameter 5 μ , were found. In three other cases macrocytosis was noted, but the size of the cells was not recorded; and in yet another case "a few megalocytes and microcytes were seen."

Immaturity and Other Variations.—Occasional erythroblasts were seen in two cases. Films were stained for reticulocytes in only a few cases, and the numbers recorded varied from nil to 4% of the red cells. Polychromasia was noted in only five cases, three being fatal. Poikilocytosis was recorded in only seven patients, being marked in two (three died, four recovered). Stippled cells were found in one fatal case and in one which recovered. Target cells were seen in four cases; three were not cases of frank jaundice.

Haemoglobin.—In some of the patients who died the haemoglobin fell to a very low level—12% in one, 14% in one, 17% in one, 20% in one, 21% in two—and was present in varying quantity up to 45 and 50% in the remainder (7) of the 13 fatal cases in which the blood was examined. In those who recovered, the lowest Hb content recorded was 17% in one case, 18% in one, 20% in one, 28% in one, and varying up to 70% in the remaining eight.

The colour index was at some time raised in the great majority of these patients, the figure varying from 1 to 1.5. In three cases only was the colour index below 1 at every count; one of these three had been ill with T.N.T. jaundice previously, one had been dosed with sulphonamide, and one had the complication of a chronic nephritis.

White Blood Cells

In the 13 fatal cases in which the blood was examined the white cell count varied from 300 to 4,800 per c.mm. (2,800 or less in eight cases), with the exception of one girl

for whom a differential cell count was done only once, the white cells numbering 6,200 per c.mm.

The white cell count in the nine patients who recovered varied up to 5,200 per c.mm., the lowest recorded being 2,000 (one case) and 2,200 (two cases).

The three cases of milder toxic anaemia showed on admission white cells of 7,400, 10,000, and 12,000 per c.mm. In each the number of white cells diminished during convalescence and recovery, although the last case (12,000), when seen one year and nine months later, was found to have 15,600 white blood cells. This young woman, however, had some chronic infection, variously diagnosed as an appendicitis and a cervicitis with pelvic infiltration.

The differential white cell count was recorded in only 12 of the fatal cases.

Polymorphonuclear Leucocytes.—These amounted to: from nil to 4% of the white cells in four cases (agranulocytosis), 7% in one case, 18-25% in six cases, and 62% in one case in which there were massive haemorrhages. In a thirteenth case it is recorded that more lymphocytes than polymorphs were seen. In the nine patients who recovered, the lowest neutrophil count varied between 28 and 84%.

Lymphocytes.—In nine of the fatal cases the highest number of the lymphocytes in the blood stream varied between 61 and 92% of the white blood cells, the average being 78%. In a tenth case it is simply stated that the lymphocytes were more numerous than the polymorphonuclears. In one case they numbered 31%; this was the woman with severe uterine haemorrhage. The number of lymphocytes is recorded in seven of the nine patients who recovered. They formed between 40 and 55%, the average being 48%. In the three milder cases of toxic anaemia the lymphocytes formed 19%, 37%, and 35%.

Monocytes.—In 10 of the fatal cases monocytes varied between 3% and 9% of the white blood cells, and in the aplastic anaemia patients who recovered, between 2 and 8%. In the three milder cases the monocytes numbered 1%, 2%, and 10%.

Bone Marrow

Records are scanty. A sternal puncture was done in only three of the fatal cases; in two of these the marrow was aplastic, while in the third the finding was inconclusive. Necropsy reports are available in 12 cases, but in only three of these was the marrow examined microscopically. Macroscopic inspection found the marrow aplastic in every case but one. The exception was that of a young woman who had died of acute purpura following jaundice, and her marrow showed a brisk haemopoiesis.

In the nine patients who recovered, sternal puncture was done in seven: in four of these the marrow was aplastic, hypocellular; in three the marrow showed a hyperplastic reaction.

It is noted that in one patient who died and in one who recovered, the hypoplasia of the marrow chiefly affected the red cells; in three who died there was a marked agranulocytosis; and in one case, also fatal, there was a marked agranulocytosis with disappearance of the platelets.

These findings tally with those of Bomford and Rhoads (1941) in their description of refractory anaemia. They state that cases of toxic anaemia, as formerly described, showed a decrease in erythrocytes, granular leucocytes, and platelets, with the red cells normal in size and shape, and an absence both of signs of regeneration and of immature blood cells; whereas it is now recognized that slight macrocytosis, small numbers of immature red and white cells in the blood, and reticulocytosis are compatible with a severely hypoplastic anaemia.

Condition of the Organs

Liver Damage.—Evidence of liver damage was found in 10 of the 15 fatal cases. Three showed acute liver necrosis at necropsy and one a subacute necrosis of the liver with nodular areas of regeneration. One had jaundice in the course of her short illness; at necropsy the liver was found

to be congested, weighing 56 oz. (1.6 kg.). One was slightly icteric on admission to hospital. In two other cases the liver could be felt two fingerbreadths below the right costal margin (no post-mortem examination in either). In two cases the liver at necropsy showed some fatty degeneration. Of the nine patients who recovered, three showed jaundice at some time. One was slightly jaundiced at the start of his illness, the liver being slightly tender, but not enlarged; another had an icteric tinge in the sclerotics, a weak positive indirect reaction to the van den Bergh test, and a persistent porphyrinuria. The latter patient was a woman who had some epigastric tenderness and whose liver seemed smaller than normal. The third was a girl whose illness started with jaundice. Concerning one other man, who recovered, having been admitted to hospital desperately ill with anaemia, it is noted that eleven months later his liver was found to be enlarged and hard. Of these 24 persons, therefore, 14 gave some evidence of liver dysfunction. The three milder cases, labelled "toxic anaemia," showed no sign of liver damage. In three of the cases noted above, the patient was first admitted to hospital on account of T.N.T. jaundice, and only when the jaundice had disappeared and the patient was apparently mending well was the injury to the bone marrow apparent, or, at any rate, appreciable.

Spleen and Lymphatic Glands.—No significant abnormalities were found in the spleen or lymph nodes of these patients. In one who died the spleen was found to be congested and weighed 4 oz. (113 g.); in another the spleen was elongated but not greatly enlarged, and it is noted that the lymph nodes were "somewhat enlarged and looked haemorrhagic." In yet another it is noted that the spleen weighed 140 g., was dark purple in colour and firm, and the Malpighian bodies were prominent. The lymph nodes were dark in colour but not much enlarged. One other patient who died had caseous tuberculous glands in the chest.

Condition of Heart.—Organic heart disease was discovered after death in one woman—slight mitral stenosis and fibrosis as of healed rheumatism. One other woman who had a blowing mitral systolic murmur showed also clubbing of the fingers. There was slight enlargement of the heart in two cases. Haemic murmurs were noted in five. In two patients the first aortic sound was weak; of these two, one died and haemorrhages were found in the heart muscle, while the other recovered.

Gastric Secretion.—A test meal was given in eight cases. One young man who died was found to have achlorhydria before and after histamine; one woman who died had a low total acidity and low HCl content; one who recovered had no free HCl and a low total acidity; in the other five cases the gastric acidity was normal or high, and, of these, four recovered and one died.

Ulceration about the Mouth and Pharynx.—This condition was present in six cases; two others had a glossitis and a ninth had preliminary dental sepsis, treated by extraction and dosage with sulphonamide.

Signs and Symptoms of Toxic Anaemia

Toxic aplastic anaemia has a most insidious onset. It should be emphasized that the expected signs and symptoms of severe anaemia may be appreciated only at a very late stage—pallor, fatigue, giddiness, breathlessness on exertion, abdominal pain. Pallor is certainly present, but may be unnoticed; fatigue and lassitude are usually present, but have not been taken as a danger signal, being the common lot in wartime. In the eagerness of wartime effort and the insistence of domestic anxieties, workers will not complain of even severe malaise. Sixteen of these persons complained of marked fatigue; they felt "always sleepy and weary," "sleepy and lifeless," "terribly tired," but the majority made such complaint *only after admission to hospital*. In the same way, 11 confessed to a shortness of breath, but most of them made this confession in a hospital bed. Cyanosis was noted only in six cases, and it was slight in all but one of them. Only one, a woman, showed the typical ashen-grey pallor of anilism. Loss of weight

may not be striking; one woman thought she had lost weight. Another, on admission to hospital, weighed 6 st. 3½ lb. (39.6 kg.), having had a serious loss of weight: she "could wrap her coat around her twice." She gained 3 st. (19 kg.) during her 14 weeks in hospital. Headache started off the illness in two cases. Paraesthesiae are not uncommon. Two patients first consulted their own doctor on account of neuritis; another complained of cramps in his legs.

It is of vital importance that the particular signs of this condition should not pass unrecognized. Most ominous and most frequently misconstrued is a complaint of bleeding from a mucous surface.

Further data concerning the present series of cases are given in Table I.

TABLE I.—Analysis of Series					
Duration of employment at work in contact with T.N.T.					
1 month	3 cases ..	2 died ..	1 recovered ..		
1-3 months ..	4 " ..	2 " ..	2 " ..		
3-12 " ..	10 " ..	5 " ..	5 " ..		
1-2 years ..	6 " ..	4 " ..	2 " ..		
Over 2 years ..	4 " ..	2 " ..	2 " ..		
Interval between last exposure to T.N.T. and start of illness					
Nil: fell sick while working ..					17 cases
Less than 1 month ..					6 "
1-3 months ..					2 "
9 " ..					1 case
18 " ..					1 "
Duration of illness					
	To date of death		To date of resuming work		
9 days ..	1 ..		—		
2-4 weeks ..	3 ..		—		
1-3 months ..	7 ..		3		
3 months to 1 year ..	4 ..		7		
1-2 years ..	—		2		
	15		12		
Ultimate cause of death					
Intractable recurring haemorrhages ..					5 cases
Thrombocytopenic purpura ..					3 "
Agranulocytosis ..					3 "
Anaemia chiefly affecting the red cells ..					1 case
Brain haemorrhages ..					2 cases
Pulmonary embolism ..					1 case
					15

A purpuric haemorrhage is often the first sign noticed by the worker. In the 15 fatal cases which occurred in the United Kingdom since January, 1940, the first signs or symptoms complained of by the worker, and sometimes the only symptoms appreciated until the terminal phase of the illness, were as follows:—(1) Haemorrhage from a mucous surface (eight cases): epistaxis, three cases (one also had bleeding gums); bleeding from gums, six cases (five were bleeding also from other sites); bleeding from uterus, three cases (also bleeding from the gums). (2) Subcutaneous capillary haemorrhages (five cases), described as "black spots," bruises, or petechiae.

In T.N.T.-workers the sign of *pallor* should never be disregarded. Any degree of pallor calls for an estimation of the haemoglobin, and if this be reduced to 80% a full differential blood count should be done. It is astonishing to what a degree of anaemia the blood may fall with no sign other than pallor.

The following findings should *ensure the temporary removal of the worker from contact with T.N.T.*: haemoglobin reading of 70% or less; white blood cells, 10,000 per c.mm. or more; lymphocytes, over 35% of the white blood cells. Monocytosis and reticulocytosis should not be disregarded.

Case Histories

Five women consulted their doctors on account of black spots or bruises on their bodies or limbs. The history of one of these is given in detail below.

Case 2

A married woman aged 24 entered a factory on July 1, 1942, and worked in and out of contact with T.N.T. until the end of 1944; perhaps 18 months in contact and 12 months in non-contact work. Before leaving the factory, on April 28, 1945, she worked part-time for 18 days, filling bombs with T.N.T. In September she began to feel short of breath. In January, 1946,

she had petechial spots on her arms, legs, and chest, and some bleeding from her gums. She consulted her doctor, but her condition was not recognized. In June she had conjunctival haemorrhages. On August 19 she was admitted to hospital. A blood count showed: red cells, 850,000 per c.mm.; haemoglobin, 21%; colour index, 1.2; white cells, 2,000 per c.mm. (polymorphonuclear cells 23.5%, lymphocytes 75%, monocytes 1.5%); platelets, 10,000 per c.mm.; reticulocytes, 0.9%. Average diameter of the red cells, 7.65 μ ; anisocytosis, some macrocytosis, slight polychromasia. She was given 11 pints (6.2 litres) of packed cells by transfusion and also received doses of "anahaemin," "benerva," pyridoxine, ascorbic acid, and "adexolin," "examen," and proteolysed liver.

On September 26 the blood showed: red cells, 3,700,000; haemoglobin, 79%; colour index, 1; white cells, 3,200 (neutrophils 42%, lymphocytes 52%, monocytes 4%, eosinophils 2%). Her heart was enlarged, the apex beat was in the nipple line and sixth intercostal space; the liver and spleen were just palpable; her gums were friable and bleeding easily, there were haemorrhages in the palate; she had had one attack of haematuria. She was discharged from hospital on October 1, but was readmitted on November 8, her condition having deteriorated. On November 21 the blood showed: red cells, 1,800,000; haemoglobin, 31%; colour index, 0.86; reticulocytes only 0.5%. Death occurred on December 26, 1946, one year and eight months after her last contact with T.N.T.

Necropsy.—Right-sided subdural haemorrhage. Pleural and pericardial effusions. Heart: petechiae in endocardium and in muscle. Liver: 2 lb. 14 oz. (1.3 kg.), showed traces of free iron. Haemorrhage in corpus luteum and in uterus. Marrow: of the sternum, good colour and consistency; of the femur, fatty degeneration. Cause of death: aplastic anaemia due to T.N.T. absorption.

In six cases epistaxis and/or bleeding from the gums was the notable symptom. Among these was the following startling case.

Case 9

This chemist, a powerfully built, well-nourished young man aged 19, joined the factory on July 8, 1940, and was employed mainly on analysis of T.N.T. samples in the laboratory, where only small quantities are handled. About once in every two months he did a three-weeks shift in the packing-houses. His duties there involved taking samples per batch from the flaking machine, an operation requiring not more than 15 seconds in possible close contact with T.N.T. dust on each occasion, the rest of his time being spent in checking the markings and general condition of the packing-cases. He never complained of feeling unwell or that the T.N.T. was affecting him in any way. Many chemists were similarly employed without receiving any appreciable harm. At the end of eight months, on March 9, 1941, he went down with influenza. On the fourth day of his illness the factory medical officer was urgently summoned and found him *in extremis*, owing to primary anaemia of unknown origin.

He was at once admitted to hospital, where he gave the history that for three months he had felt easily tired and short of breath, that his nose had been bleeding frequently, and that he was constipated. On March 12 the blood count showed: red cells, 1,380,000 per c.mm.; haemoglobin, 28%; colour index, 1.01; white cells, 1,200 per c.mm. Blood transfusions were started and daily injections of "hepatex." He received also vitamins B and C and intramuscular calcium and "kapilon." On March 26, having had 3 pints (1.7 litres) of blood altogether, his condition had improved, but haemorrhages were found in both retinae. By April 3 he was able to leave his bed. Repeated transfusions had by April 16 brought his red cells up to 4,160,000; haemoglobin, 50%; colour index, 0.71. Agranulocytosis, however, was extreme, the polymorphonuclear cells being only 7%, lymphocytes 83%. On May 10 he was improving; there had been no epistaxis for two weeks. He had been given physical exercise and ultra-violet baths. Almost at once, however, the haemorrhagic phase of his illness set in, the bleeding from the nose and gums becoming uncontrollable. On May 14 the blood showed: red cells, 1,370,000; white cells, 1,500. No platelets could be found. Pentnucleotide injections were given daily from May 16 to 21. He was now covered with purpuric spots from head to foot. A histamine test meal showed achlorhydria before and after the administration of histamine. A van den Bergh test was negative. He received in all some 22 pints (12.5 litres) of blood by transfusion, but died from platelet deficiency on May 31, 1941, eleven and a half weeks from the start of his illness.

Necropsy.—There were widespread petechiae and ecchymoses. The liver seemed healthy but had a rusty look, suggesting haemo-

siderosis. The mesenteric glands were somewhat enlarged. Marrow: in the ribs, red; in the lumbar vertebrae, more scanty, but red; in the femur, entirely yellow and fatty. Cause of death: aplastic anaemia due to T.N.T.

Another patient, whose illness began with bleeding from gums, recovered after numerous blood transfusions.

Case 12

A woman aged 28 entered a factory on March 13, 1941. She was in and out of contact with T.N.T. until the first week of January, 1942, except for three weeks in October, 1941, when she was given non-contact work because she complained of fatigue, shortness of breath, and poor appetite; at the end of three weeks she felt perfectly well and returned to contact work. On January 1, 1942, she stayed at home on sick leave. On January 26 she was admitted to hospital. There she gave a history that her gums had been bleeding for the past month; that she had had one attack of vomiting; that for three months she had been lacking in energy, and this was getting worse; that if she hurried she got palpitations and a feeling of breathlessness; that two months previously she had a heavy "period." On January 28 a blood count showed: red cells, 850,000 per c.mm.; haemoglobin, 20%; colour index, 1.25; average diameter of red cells, 7.8 μ ; white cells, 3,800 per c.mm. (neutrophils 57%, lymphocytes 41%, monocytes 2%); anisocytosis, macrocytosis; cells well stained, no immature whites seen.

On February 3 she was found to have retinal haemorrhages. The icterus index was 10 units, the van den Bergh reaction negative, Webster's test negative. Three days later the red cells had dropped to 730,000; haemoglobin, 17%; colour index, 1; white cells, 5,100 (neutrophils 43.5%, lymphocytes 51%, monocytes 3.5%, eosinophils 1.5%, basophils 0.5%). The marrow, by sternal puncture, showed: polymorphonuclears, 16%; preleucocytes, 18%; myelocytes, 34%; primary erythroblasts, 2%; secondary erythroblasts, 4%; normoblasts, 1%; lymphocytes, 25%.

Comment by Dr. C. V. Harrison: "The blood picture shows a very severe normocytic anaemia. The marrow picture indicates a severe depression of erythroblastic haemopoiesis. The appearance of the case as a whole suggests an aplastic anaemia, particularly affecting the red cells."

The clinical note at this time states: "Feels fine. Looks terrible." Next day the patient had a uterine haemorrhage, and a blood transfusion produced a severe rigor. Fresh haemorrhages appeared in the retinae. Two further blood transfusions were helpful. She was given another 11 pints (6.2 litres) of blood (on five occasions), and was allowed to go home on March 23 to attend every second day for liver injections and to have a weekly blood count. At this time her red cells numbered 4,800,000; haemoglobin, 76%; colour index, 0.8. On May 14 her blood had dropped again to: red cells, 1,800,000; haemoglobin, 38%; colour index, 1.06. She was readmitted to hospital, given three more transfusions, and sent home again on June 20, to attend as before.

On February 5, 1943, a blood count showed: red cells, 4,210,000; haemoglobin, 90%; colour index, 1; white cells, 5,200 (polymorphonuclear 65%, lymphocytes 32%, monocytes 1%, eosinophils 1%, basophils 1%); red cells normal in size and staining. On March 27, 1945, she was well. Blood count: red cells, 5,024,000; haemoglobin, 100%; colour index, 1.0; white cells, 10,000 per c.mm.; red cells normal in size, shape, and staining, no immature reds seen. On May 8, 1946, the blood showed: red cells, 4,000,000; haemoglobin, 85%; colour index, 1.06. She then attended fortnightly for injections of liver and was given iron by mouth. On August 6 a final note says: "Recovered and well." During her illness, in addition to the transfusions, she had received: ferri et ammon. cit., "neohepatex," vitamin C, "campolon," anahaemin, "jactemia," and "betaxan."

Another case of the series was marked by severe uterine haemorrhage.

Case 13

A woman aged 27 entered the factory on February 5, 1942. There was no history of previous illness. She worked in contact with T.N.T. for nine and a half months, never missing a day's work except once when she missed the bus. She attended the routine inspections regularly, never complained, and was recorded as fit. On November 22 she stayed at home, her doctor's certificate stating: "colic"; and a week later, "anaemia and debility." On December 2 she was admitted to hospital on account of uterine haemorrhage, so severe that abortion was suspected. The uterus was explored and emptied—of blood clot only. A blood count showed: red cells, 630,000 per c.mm.; haemoglobin, 12.5%; colour index, 1.0; mean corpuscular

volume, 95 μ^2 ; white cells, 3,000 per c.mm. (polymorphonuclears 62%, lymphocytes 31%); bleeding-time increased, but not coagulation time. A sternal puncture was done, but the findings were inconclusive. Treatment with liver and iron had no effect. She was given repeated transfusions, but her temperature rose steadily, and she died on January 2, 1943.

Necropsy.—Extreme pallor. Marrow of sternum, femur, and one rib was uniformly yellow except for a faint pinkish colour in the femur. Uterus small and full of clot. Other organs normal except for pallor. Cause of death: aplastic anaemia due to T.N.T. The factory was not informed of the illness until after the post-mortem examination had been made.

The history of the first known case in the United Kingdom of recovery from aplastic anaemia due to T.N.T. was as follows:

Case 14

A married woman aged 36, six children, entered a factory early in August, 1940. She worked for three weeks out of contact, for three weeks in light contact, on filled shells, and then in full contact in the shifting-house. On November 18, after about nine weeks in contact with T.N.T. as shift-house attendant, she reported to the factory medical officer on account of dizziness and weakness, loss of appetite, and loss of weight; she complained also of vomiting and of xiphisternal pain. Her complexion was very sallow, with a suggestion of jaundice; she had icterus of the sclerotics and ulcers in the mouth. The liver seemed smaller than normal, the urine contained bile and gave a positive Webster reaction. She was admitted to the Cardiff Royal Infirmary the same day, under the care of Professor A. M. Kennedy, to whom I am much indebted for the use of his personal notes. On admission she confirmed the history given above, adding that she had some shortness of breath and palpitation, and that her urine had become dark in colour, "like strong tea"; she had not felt well for about a month and had the constant bitter taste of T.N.T. in her mouth. She had had amenorrhoea since February, 1940. Her weight was 6 st. 3½ lb. (39.6 kg.).

Examination showed a very thin woman, with ashen-grey pallor of lips, pale sallow complexion, but no jaundice; a bald tongue with small ulcers beneath it, and some abdominal tenderness. The liver and spleen were within normal limits, the stools normal in colour. Van den Bergh: negative direct but weak positive indirect reaction; icterus index, 5 units; Kahn negative; no methaemoglobin found. A blood count showed: red cells, 2,620,000 per c.mm.; haemoglobin, 70%; colour index, 1.3; white cells, 3,200 per c.mm. (polymorphonuclears 44%, lymphocytes 50%, monocytes 5%, myelocytes 1%); the cells were toxic, lymphocytes and polymorphonuclears containing dark granules; numerous megalocytes and few microcytes, no poikilocytes, no polychromasia; a very occasional reticulocyte on searching; platelets, 52,000 per c.mm. Urine: Webster reaction positive on admission and for the next nine days. Porphyrinuria was present (+ +) throughout her stay in hospital and then gradually lessened, to disappear at the 27th week from the start of her illness. A very faint trace of albumin during her last week in hospital. Fractional test meal showed the acid content of her stomach to be low; no free HCl present.

Progress.—On admission to hospital she was gravely ill. During her stay of 14 weeks, from November, 1940, to February 21, 1941, her general symptoms soon abated, though her blood improved but slowly. Just before leaving hospital the blood count was almost normal; she looked and felt very well and had put on over 3 st. (19 kg.) in weight. Blood examination: red cells, 4,560,000; haemoglobin, 92%; colour index, 1.01; white cells, 8,200; platelets, 228,000. After leaving hospital she attended at first weekly, and then fortnightly, for 21 weeks, until her confinement in November, 1941. This confinement was normal, and she nursed the baby for a year without any setback to her health. She again attended from time to time until the summer of 1943, when she was once more advanced in pregnancy, expecting her eighth child.

Treatment.—Neohepatex, either 2 or 4 ml. intramuscularly, was given three times a week, for one month, total 40 ml.; then, anahaemin, 2 ml. intramuscularly, three times a week for five weeks, then daily for one week; then, ventriculin, 30 g. daily by mouth, from February 4 to the end of October, 1941, when she entered a maternity home. On leaving the home, on November 18, she again took ventriculin until just before Christmas. For one month during her pregnancy she received ferri et ammon. cit., 30 gr. (2 g.) t.d.s., and again while in the maternity home. While in the home she was also given campolone.

Two women developed aplastic anaemia following T.N.T. jaundice. The case history of the first is given below.

Case 15

A woman aged 26 who had always enjoyed good health entered a factory on October 19, 1940. She worked in contact with T.N.T. until November 14 (just under four weeks). She then sprained her wrist and was given light non-contact work for one month. On December 16, on attending the factory surgery because of her wrist, she was seen to be jaundiced, her liver was enlarged, there was bile in her urine, and she had some abdominal tenderness and pain. She was admitted the same day to the Cardiff Royal Infirmary under the care of Professor A. M. Kennedy, to whom I am indebted for the use of his personal notes.

On admission she said she had felt quite well until the beginning of December, when she had been on night shift for about a week. She then began to feel sick and averse to any food. She had no vomiting, no headache, no dizziness. She began to have two or three loose greyish motions a day, and epigastric pain; the urine darkened in colour and her eyes became slightly yellow. Her menstrual period, due on December 11, did not occur.

Examination showed she was thin, weighing 6 st. 11½ lb. (43.3 kg.), with slight general icterus, tongue moist, no ulceration in mouth, lips slightly cyanosed. Heart: first aortic sound weak. Nothing else amiss in chest. The liver could be felt 1 in. (2.5 cm.) below the costal margin, in nipple line. Tenderness was present in epigastrium and over ascending and descending colon. The van den Bergh reaction was biphasic; icterus index, 35 units; Kahn negative; no methaemoglobin found. During the next three weeks her general condition steadily improved; by January 21, 1941, she was looking well and feeling very well. She had put on weight, the jaundice was practically gone, and no cyanosis was to be seen. She was enjoying her food; weight, 7 st. 6 lb. (47.2 kg.).

On January 28 she felt all right, but her skin was pale and unhealthy-looking and she was perspiring freely. The liver had increased in size until the margin could be felt halfway between the ensiform and the umbilicus. The red blood cells were becoming megalocytic. On January 31 the terminal phase of her illness set in: her temperature rose high, her mouth showed gingivitis with necrotic patches around the bases of the teeth, there were submucous haemorrhages on the lower lip and tip of tongue, the tongue was thickly coated and the pharynx reddened. Soon the gums were bleeding freely and there was subconjunctival haemorrhage. She received 1 pint (570 ml.) of blood by transfusion without relief, and on February 5 she died. The blood counts are shown in Table II. No megaloblasts seen; practically no poikilocytosis, no polychromatophilia. Variation in size was the feature of the film, but the variation was in an upward direction. An occasional cell was about 6 μ in diameter, many were 10 μ and up to 12.5 μ , and some were fully 15 μ . Nucleated red cells were not seen.

TABLE II.

Date	Red Cells per c.mm.	Hb %	C.I.	White Cells per c.mm.	Polymorphs %	Lymphocytes %	Monocytes %	Eosinophils %	Pre-mycytes %	Platelets per c.mm.
17/12/40	5,100,000	92	0.90	5,000	70	22	7	1	—	132,000
24/12/40	5,000,000	98	0.98	8,000	67	28	4	1	—	140,000
31/12/40	4,900,000	96	0.98	7,200	67	28	3	1	2	147,000
7/1/41	4,320,000	92	1.07	5,200	52	43	2	1	2	129,600
14/1/41	4,060,000	90	1.12	4,400	34	59	4	1	2	81,200
21/1/41	3,650,000	90	1.23	3,200	31	63	4	1	1	51,100
28/1/41	3,070,000	74	1.23	4,400	7	67	5	1	—	30,700
3/2/41	2,010,000	50	1.25	2,000	0	84	4	0	7	8,040

On January 28 lymphoblasts were present, and on February 3 Türk's irritation cells (5%).

Urine.—Webster reaction negative throughout. For the first three weeks there was a very faint trace of albumin. For two and a half weeks bile pigments were present, and then urobilinogen for five days. No urobilin was found. Porphyrinuria was present—a heavy deposit for the first three weeks, then variable. An ether-soluble deposit was present for 18 days from the start of the fourth week, reappearing before death.

Necropsy.—Necrosis of the liver. Widespread purpuric haemorrhages in the skin and mucous and serous membranes. Ulceration of tongue. Congestion of lungs, with oedema of lower lobes and partial collapse of lower lobe of left lung.

"Dust cells" more numerous than normal. The heart showed numerous haemorrhages in the pericardium and in the muscle; the aorta was small, with some fibrosis and stenosis at the point of entry of the ductus arteriosus. The femur contained red gelatinous marrow in the upper half of the shaft. The lymph nodes were not greatly enlarged, they contained much brown pigment, mostly in phagocytic cells.

Six cases were admitted to the Royal Infirmary, Salford, under the care of Professor R. E. Lane, to whom I am indebted for the use of his reports. All these patients recovered. The histories of two were as follows:

Case 19

A young woman aged 21 entered a factory on March 4, 1942, and worked for three months in contact with T.N.T. On June 7 she was found to be deeply jaundiced. She gave a history that two weeks previously she had caught a bad cold and that for the past week she had had pain in her stomach, with sickness and jaundice. On admission to Salford Royal Infirmary next day she was deeply jaundiced, the van den Bergh test gave a positive direct reaction, the serum bilirubin amounting to 29 mg. per 100 ml. Bilirubin was present in the urine and there was a slight excess of urobilin. A laevulose-tolerance test was slightly abnormal (low starting and finishing figures). A blood count showed: red cells, 4,500,000 per c.mm.; colour index, 1.15; mean diameter of red cells, 8 μ . She was discharged home on July 24, her serum bilirubin still 5 mg. per 100 ml., still jaundiced, haemoglobin 76%. She had gained in weight and was feeling well. One month later (August 27) she reported at the factory, feeling very tired. The conjunctivae were still jaundiced, her lips and mucous membranes very pale, her feet swelling. She was sent to hospital by ambulance. Blood showed: red cells, 1,040,000; haemoglobin, 28%; colour index, 1.4; mean diameter of red cells, 7.4 μ ; white cells, 3,000 (polymorphonuclears, 28%); platelets, 450,000 per c.mm. She was immediately given 3 pints (1.7 litres) of whole blood, then treated with rest, iron, full diet with added vitamins. Her blood deteriorated, and she again received transfusion, and was allowed to go home on October 7. On November 14 she was readmitted to hospital. Blood showed: red cells, 1,900,000; haemoglobin, 60%; mean diameter of red cells, 7.8 μ ; colour index, 1.6; white cells, 5,600 (polymorphonuclears 28%). Sternal puncture found marrow which was active and cellular, but with inversion of the erythromyeloid ratio; the red cells were extremely large. Once more she was transfused, and sent home for a month. From this time she steadily recovered and was able to return to non-contact work on January 11, 1943. On December 1, 1943, a blood count showed: red cells, 4,400,000; haemoglobin, 104%; colour index, 1.18; mean diameter, 7.6 μ ; white cells, 5,900 (polymorphonuclears 50%). On November 26, 1946, her doctor wrote that she was in a state of advanced pregnancy and "looking as fit as can be."

In the second case illness started 18 months after a very short period of contact with T.N.T.

Case 24

A man aged 46 entered a factory on December 28, 1939, and worked in full contact with T.N.T. for only five weeks, from July 6 to August 8, 1940. He was then taken permanently out of contact. He complained that he was short of breath, had a poor appetite, and felt lifeless. He was cyanosed and pale. His symptoms subsided, and he remained well until February 7, 1942, when he reported to his own doctor on account of neuritis. His pallor was noticed, but he said he felt fine. On March 19 he was admitted to hospital in a state of aplastic anaemia. He was pale but cheerful; there was no wasting, and no symptoms except that he felt short of breath on exertion. A blood count showed: red cells, 1,700,000 per c.mm.; haemoglobin, 35%; colour index, 1; mean diameter, 7.5 μ ; white cells, 4,800 per c.mm. (polymorphonuclears 51%). The van den Bergh reaction was negative; serum bilirubin, 0.6 mg. per 100 ml. Sternal puncture showed a markedly cellular marrow, lymphocytes predominating, with a few normoblasts and myelocytes. He was treated with repeated transfusions of blood, up to 4 pints (2.3 litres) at a time, until October, 1943. By this time he had received 37 pints (21 litres) of whole blood, and he gradually recovered. On January 26, 1944, a blood count showed: red cells, 2,500,000; haemoglobin, 66%; colour index, 1.3; mean diameter, 8 μ ; white cells, 6,200 (polymorphonuclears 52%). Further treatment with vitamins B and C was given and his butcher was asked to provide him whenever possible with liver, tripe, and hearts. In July, 1944, he started light work, out of contact.

Treatment

Early and complete removal from contact with T.N.T. is the first essential. Blood transfusions were given in 19 of the 24 cases of aplastic anaemia. Four of these patients were given packed cells; for the other 15 whole blood was used. The dosage varied from 500 ml. to 4 pints (2.3 litres). The largest total quantities given were: 46 pints (26.1 litres) over a period of 12 months to a man who eventually recovered; 37 pints (21 litres) over a period of 18 months, 23 pints (13 litres) over 3½ months, both patients surviving; 22 pints (12.5 litres) over 11½ weeks to a man who died.

Liver preparations, iron, and vitamins B, C, K, and P were all freely given. Pentnucleotide was prescribed in four cases.

Of the four patients who did not receive transfusion three recovered, one died without admission to hospital. In one case the hospital records have been destroyed.

It is clear that treatment by blood transfusion needs to be adjusted with great care. It is generally agreed that no attempt should be made to restore the blood cell count or the haemoglobin content to normal levels, for the haemopoietic function of the bone marrow may be depressed by such massive donations. The object must be to maintain a blood level sufficient to support life, with a safety margin, until the haemopoietic tissues recover from their intoxication and resume their proper duty of supplying cells to the blood. Bomford and Rhoads (1941) suggest, further, that an increased rate of haemolysis may follow excessive transfusion; it is indeed surprising how quickly, after transfusion, the blood can revert to its former poor condition. These authors state that patients who have been ill for some time are usually comfortable in bed with a Hb level of about 30%; patients up and about usually require to be kept at a slightly higher level. The method they recommend as ideal is to give not more than 500 ml. of blood at a time—whole, unaltered, fresh blood from a donor of identical group—and to give rapidly by a multiple syringe method. Post-transfusion reactions, they say, are thus reduced to a minimum.

This has not been precisely our experience. Professor R. E. Lane, whose six successful cases are in this series, made it his practice to give larger quantities of blood, at longer intervals. The initial transfusion was of 2 or 3 pints (1.1 or 1.7 litres) and, with convalescence, the patient was filled up with 3 or even 4 pints (1.7 or 2.3 litres) at a time and then sent home for a month or longer, to return for examination and repeat treatment if the blood level had not been naturally maintained. A haemoglobin level of not more than 60% was found to be adequate. While the blood level was thus maintained, restoration of haemopoiesis was encouraged by the administration of liver, iron, vitamins B, C, and K, and, in one case without transfusion, ventriculin (Kennedy and Ingham, 1942).

Eddy (1944) emphasizes the importance of giving fresh blood, not more than 24 hours old, to secure the value of the short-lived white cells and platelets.

It was inevitable that transfusion reactions should have appeared in several of the cases, for they occurred from 9 to 13 years ago, when the Rh factor (discovered in 1940) was not yet fully known, and any blood transfusion was somewhat of a venture. A determination of the Landsteiner group (ABO) was usually, but not necessarily always, followed by bedside matching, and reactions were not infrequent. One woman, group A, was given 5 pints (2.7 litres) of blood, and for this purpose 16 donors were brought in, 14 of them of group A and two of group O. She matched only with the two group O bloods and with three of group A. Difficulty was experienced at times in finding a suitable vein, as not all house-physicians were expert in the technique. Details are not recorded in most cases, but in some the blood was given by slow drip. To illustrate the difficulties it may be stated that the diagnosis "toxic rash" on a sick certificate brought the factory medical officer out post-haste to see an employee who had been admitted to hospital. The patient was found to be in a state of grave

anaemia, but he had to be removed to another hospital for treatment, because never in the history of the first hospital had a blood transfusion been given.

Summary

Twenty-four cases of aplastic anaemia caused by the absorption of trinitrotoluene (15 being fatal) are recorded. Of the nine patients who recovered, six were treated by multiple blood transfusions with administration of liver, iron, and vitamins; three received liver, iron, and vitamin therapy, but no blood transfusion; one of these three also received ventriculin.

Analysis is made of these 24 cases and of three cases of early toxic anaemia due to the same cause. The insidious onset of aplastic anaemia sets a difficult problem.

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An interim statement has been made to the Minister of Health, Mr. E. A. NUGAWELA, by Mr. DONALD BARLOW and Professor ROBERT NEUBAUER, of the World Health Organization, and Professor JOHN CROFTON, of Edinburgh, on the progress made by the Ceylon Government in implementing Mr. Barlow's recommendations, made in 1952, for reorganizing the campaign against tuberculosis. On returning to Ceylon, states the report, Mr. Barlow was forcibly struck by the many improvements which had occurred. Great strides had been made in both prevention and cure. The team felt that there was still a long way to go, but the Government had attacked the problem with vigour and determination. No Government could have been more alert to its responsibilities. The report draws attention to the enthusiasm of those taking part in the scheme, noting that the hopelessness on the faces of the patients in the grossly overcrowded and ill-equipped wards had given place to hope, cheerfulness, and expectation of recovery. X-ray facilities are being increased, and a start has been made in the provision of pathological and bacteriological services. Since 1952 the mortality from diagnosed tuberculosis has been halved. This is attributed partly to the provision by the Government of large funds for the purchase of modern drugs. The training of doctors and nurses still presents a big problem. A fair number have taken advantage of the Colombo Plan Scheme of training in England, but at least one more fully staffed and equipped medical school is required in Ceylon.

THE EFFECT OF INSULIN ON NITROGEN RETENTION IN THE HYPOPHYSECTOMIZED RAT

BY

R. T. B. LAWRENCE, B.Sc.(Med.)

Research Assistant, Department of Physiology

JAMES M. SALTER, M.A.

Research Associate, Department of Physiology

AND

CHARLES H. BEST, M.D., F.R.S.

Director, Department of Physiology, and Banting and Best Department of Medical Research

University of Toronto, Toronto, Canada

It has been reported from this laboratory that exogenous insulin promotes growth in hypophysectomized rats.^{1,2} These animals gain weight owing to increases in protein, fat, and water. The observed increases in body protein stimulated us to study in some detail the effect of insulin on nitrogen retention.

Procedure

Male rats with an average body weight of 119 g. which had been hypophysectomized 14 days previously were used in all experiments. The animals were maintained in a constant-temperature room at 28° C. In Experiment A the daily nitrogen balances of six untreated hypophysectomized rats were determined for a 12-day period. In Experiment B hypophysectomized rats were divided into one control group of 12 animals and one experimental group of eight animals. Nitrogen-balance studies were not performed on the controls, but a good indication of the balance maintained by these animals during the experimental period was secured by determining changes in the nitrogen content of their carcasses. This observation was made by sacrificing six of the rats on the initial day of the experiment and comparing their average total body nitrogen with a similar value obtained from the remaining six controls sacrificed on the last day of the experiment.

The daily nitrogen balance of each of the eight rats in the experimental group was determined for (a) an initial period of three days before insulin was administered; (b) an intermediate period of seven days during which each rat received one daily injection of increasing amounts of protamine zinc insulin; and (c) a four-day period following the cessation of insulin treatment. These rats were sacrificed with surviving members of the control group on the fourteenth day. Total body nitrogen determinations were made on each carcass. The nitrogen balance was regarded as the difference between nitrogen ingested and nitrogen excreted in the faeces and urine.

The food mixture consisted of the following ingredients: water, 1,200 ml.; "Chum" dog food, 890 g.; dried white bread crumbs, 335 g.; powdered skim-milk, 145 g. The glucose was dissolved in the water and this solution used to reconstitute the powdered milk. The remaining constituents were thoroughly mixed in and the whole was homogenized in a Waring blender.

Dry-weight determinations were made on nine samples of the diet. The nitrogen contents of these dried samples were determined. The results agreed very closely and showed that the diet was well homogenized.

All rats ate *ad libitum*. To avoid errors due to evaporation, the amount of food given each rat daily was calculated in terms of its dry weight. The food remaining from the previous day was removed and dried to constant weight. The dry weight of the food eaten was then determined and