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ANAEMIA ASSOCIATED WITH TRAUMA AND SEPSIS*

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Since the Goulstonian Lecturer in 1932 took as his subject the "pathology and treatment of anaemia" great advances have been made in our understanding of the aetiology and treatment of many blood diseases. There are, however, two extremely common anaemias the cause of which remains obscure and the treatment unsatisfactory—namely, the anaemia found in association with infection and the anaemia found in association with trauma.

My reasons for considering these two conditions together are: (1) The morphological character of the anaemia is the same and there are striking similarities in the metabolic findings. (2) There is no effective treatment of the anaemia beyond supplying already matured red cells in the form of transfusions while awaiting improvement in the underlying infection or healing of the injured tissues. (3) The available evidence suggests that in both conditions the synthesis of haemoglobin is in some way at fault and that this failure of haemoglobin synthesis is responsible for the anaemia.

In discussing the anaemia both of trauma and of infection it must be remembered that in recent years the picture has almost invariably been complicated by treatment with the sulphonamides, which may themselves affect haemopoiesis (Rimington, 1939). Further, trauma is likely to be complicated by infection, and in some instances the reverse may occur—for example, the presence of osteomyelitis or empyema may necessitate operative intervention. However, relatively simple cases of each have been recorded (Saifi and Vaughan, 1944; Howard, 1945) in which anaemia is still found.

Anaemia of Sepsis: Morphological Characteristics

In considering the morphological character of anaemia associated with sepsis it is probably important to differentiate between acute and severe infections and more chronic infections, though it is difficult to know how best to make the distinction. In a previous study (Saifi and Vaughan, 1944) the presence of an infection of longer than three months was regarded as chronic, while anything less than three months was regarded as acute. It might be wiser to make the distinction depend rather on the virulence and nature of the infectious process than on its duration.

Anaemia Associated with Virulent Infection

In certain fulminating infections, such as with *Clostridium welchii*, the anaemia is certainly haemolytic and often megalocytic. Other scattered examples of proved haemolytic anaemia associated with severe infection characterized

by a high colour index and sometimes increased red-cell fragility have been described (Brown *et al.*, 1944; Mollison, 1947). Such cases, however, occur as interesting rarities meriting special description. Mollison (1947) reported two unusual cases of hyperchromic anaemia and sepsis—one associated with advanced bilateral tuberculosis, the other with acute osteomyelitis. In both the anaemia was severe—in one there was increased red-cell fragility, in the other it was not recorded. A few similar cases associated with severe sepsis in burns have been described (Brown *et al.*, 1944). Rare cases of hyperchromic megalocytic anaemia unassociated with lesions of the gastro-intestinal tract have also been reported in tertiary syphilis (Tauber and Goldman, 1935).

Blackfan and Diamond (1944) observed 15 infants between the ages of 4 and 16 months in whom a severe megalocytic anaemia developed in association with acute infection and was corrected by the parenteral administration of liver extract. In only one was a prolonged course of liver therapy needed. The remaining children recovered completely after a single course of treatment. The anaemia was associated with a temporary complete achlorhydria. Unfortunately no details are given. Since the anaemia responded to treatment apparently in the presence of infection, it seems possible that it was primary in origin, though even in primary anaemias infection often has an inhibiting effect on the action of haemopoietic factors. Zuelzer and Ogden (1946) reported 26 presumably similar cases in infants 2 to 11 months old in which the bone marrow resembled that of pernicious anaemia—megaloblasts and giant metamyelocytes being present in large numbers. The anaemia was not always megalocytic, but was often associated with leucopenia, neutropenia, and thrombocytopenia. Such cases responded to folic acid or liver extract. It is, however, not altogether clear whether the anaemia followed the infection, or vice versa.

The anaemia associated with *Brucella* infections also merits special mention. It has been recorded by Calder *et al.* (1939) as being macrocytic and hyperchromic, and by Harris (1941) as being sometimes like pernicious anaemia. I have seen it on at least four occasions with a high colour index and young red and white cells in the peripheral blood—in fact, a leuco-erythroblastic type of anaemia, which caused considerable confusion in diagnosis. Characteristically it is of the normocytic hypochromic type (Cartwright *et al.*, 1946a).

Anaemia Associated with Chronic Infections

The anaemia associated with chronic or non-fulminating infections is normocytic and normochromic in the majority of cases, though it may become somewhat microcytic and

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hypochromic if the infection is of long standing. In 24 cases of infective endocarditis Pepper (1927) recorded a hypochromic type of anaemia associated with both a *Streptococcus viridans* and a haemolytic streptococcal infection. Horder (1926) alone claimed to have found a high colour index in infective endocarditis, but he gave no numerical data. In tertiary syphilis moderate hypochromic anaemia may occur, particularly in untreated cases. It is less pronounced than in the primary and secondary stages (Rosahn and Pearce, 1934; Tauber and Goldman, 1935).

In rheumatic fever the cell size, the mean corpuscular haemoglobin, and the mean corpuscular haemoglobin concentration in one large series varied from low to normal values (Hubbard and McKee, 1939). In chronic rheumatic conditions, especially in women, a hypochromic type of anaemia is common, and is often but not necessarily associated with achlorhydria (Collins, 1935). The severer grades are found in cases of atrophic rheumatoid or infective arthritis.

Josephs (1936) stated that in infants the anaemia tends to be hypochromic and that extreme hypochromia is rare. Blackfan and Diamond (1944) also described a microcytic hypochromic anaemia in infants and a mixed type showing microcytosis and macrocytosis, the latter responding to liver and to iron after recovery from the infectious process, suggesting that there is a deficiency of both.

Rasmussen (1936), reviewing the blood picture in 460 patients with pulmonary tuberculosis, noted a hypochromic type of anaemia in 12% of cases. In 34 non-febrile cases the anaemia responded to liver therapy. In 13 there was widespread tuberculosis involving the intestinal canal, presumably therefore interfering with intestinal absorption. In 10 cases other forms of infection, such as with haemolytic streptococci, were present. Braverman (1938, 1942), from a review both of his own cases and of the literature, concluded that the anaemia in tuberculosis, if present, is usually mild, most commonly hypochromic and microcytic, but sometimes normochromic and normocytic. He found such anaemias in 46% of a series of 509 patients.

Saifi and Vaughan (1944) in 34 cases and Cartwright *et al.* (1946a) in 16 cases of anaemia associated with such infections as osteomyelitis, empyema, infective endocarditis, chronic nephritis, and pneumonia failed to find a macrocytic type of anaemia. The anaemia was mild, normocytic, and normochromic, or slightly microcytic and hypochromic. In a series of 464 cases Wintrobe (1934) found no case of a megalocytic type of anaemia, and hypochromia was observed only in association with blood loss or nutritional deficiency. The anaemia was normocytic or slightly microcytic. Under experimental conditions in animals an anaemia with exactly the same morphological features is produced by the injection of bacteria or by the production of a sterile abscess by turpentine (Robschey-Robbins and Whipple, 1936; Cartwright *et al.*, 1946b). The injection of bacterial toxins alone does not cause anaemia, suggesting, as will be discussed later, that the essential factor in infections responsible for the anaemia is inflammatory tissue reaction.

Bone Marrow.—The accounts of bone-marrow findings in anaemia associated with sepsis are largely unsatisfactory, as only very partial examination of the skeleton is usually made. In both acute and chronic infections in which we examined the long bones from arm and leg and wedges from sternum, vertebral column, and pelvis we found active marrow often in excess of normal. All patients showed considerable erythroblastic activity though there was excessive leucopoiesis. In some instances there was myeloid activity of the spleen (Saifi and Vaughan, 1944).

Metabolic Characteristics of the Anaemia of Sepsis

In recent years there has been an increasing amount of data concerning what may be described as the metabolic characteristics of the common anaemia found in association with sepsis.

Serum bilirubin is within normal limits (Vaughan and Saifi, 1939; Saifi and Vaughan, 1944; Cartwright *et al.*, 1946a).

Plasma iron is low (Heilmeyer and Plötner, 1937; Schafer, 1940; Hirvonen, 1941; Bröchner-Mortensen and Stein, 1942; Cartwright *et al.*, 1946a). The fall in plasma iron immediately follows the infectious process even in those cases in which no anaemia develops. The normal range for humans is 120 ± 30 $\mu\text{g. per 100 ml.}$, while in 16 cases of anaemia associated with infections recorded by Cartwright *et al.* (1946a) the values ranged from 15 to 40 $\mu\text{g.}$ The hypoferræmia persists so long as the infection continues, and returns to normal more slowly than the haemoglobin or red cells.

Serum Copper.—On the other hand the serum copper is raised. The normal range determined by Cartwright *et al.* (1946a) was 116 ± 20 $\mu\text{g. per 100 ml.}$ The value in the 16 patients already mentioned was 200–262 $\mu\text{g.}$ with two exceptions.

Erythrocyte Protoporphyrin.—This porphyrin—protoporphyrin type III, from which haematin is formed by conjunction with iron—was with one exception increased in 11 cases studied by Cartwright *et al.* (1946a). The normal range is 20–50 $\mu\text{g. per 100 ml. of red cells.}$ In the patients studied it was increased two to fourteen times above normal, reaching a maximum in one instance of 634 $\mu\text{g. per 100 ml. of red cells.}$ This rise occurs slowly during the development of anaemia and returns slowly to normal after recovery.

Urinary and Faecal Coproporphyrin.—Vaughan and Saifi (1939) recorded an increase of both coproporphyrin I and III in the urine: an average of 427.1 $\mu\text{g. daily}$ was found in one patient; in another there was an increase of coproporphyrin I with only a trace of III; in a third there was an increase in urinary porphyrin but not enough for identification. The faecal porphyrin consisted of a chloroform-soluble fraction (protoporphyrin deuteroporphyrin) and an insoluble coproporphyrin fraction containing coproporphyrin III. Cartwright *et al.* (1946a) also reported an increase in urinary coproporphyrin but did not differentiate the type. A similar increase in coproporphyrin III excreted in infections in the urine has been noted by Rimington and Hemmings (1938), by Curphey and Solomon (1938), and by Watson and Larson (1947), particularly in acute poliomyelitis. The last-named workers recorded an increase of coproporphyrin I in certain infections, particularly infectious hepatitis.

Faecal Urobilinogen.—There are relatively few data available on urobilinogen excretion in anaemia associated with infection. Eppinger and Charnas (1913) noted a normal figure in a patient with anaemia and pulmonary tuberculosis. Bauman (1921), using a rather unsatisfactory method of estimating, recorded normal figures in two cases of infectious endocarditis. Weiss (1930) noted a patient with tuberculous glands who excreted 56 $\mu\text{g. of urobilinogen daily}$ and three cases of pulmonary tuberculosis with figures ranging from 54 to 132 $\mu\text{g. daily.}$ Paschkis (1933) recorded a case of infective endocarditis with a daily excretion of 228 $\mu\text{g.,}$ and Heilmeyer and Plötner (1937) quoted a case of rheumatic polyarthritis with an absolute excretion of 77 $\mu\text{g. daily.}$ Watson (1938) recorded a patient with chronic infectious arthritis in whom the excretion was 60 $\mu\text{g. daily.}$ Our own series of eight cases, the largest available, showed no increase above normal in seven patients and in the eighth an increase so slight as to be insignificant, the upper figure for normal in men being taken as 280 $\mu\text{g.}$ (Vaughan and Saifi, 1939). The same results were obtained when excretion was related to the total circulating mass of haemoglobin rather than expressed in absolute amounts.

Urobilinogen in Urine.—We (Vaughan and Saifi, 1939) observed no increase in urinary urobilinogen, but increases have been noted by other workers (Harris, 1927; Weiss, 1930; Watson, 1938; Curphey and Solomon, 1938; Hubbard and McKee, 1939).

Plasma Proteins.—In the series of cases investigated by Cartwright *et al.* (1946a) the plasma proteins were within the

normal range, varying from 5.9 to 7.4 g.% and in those patients examined the relative proportions of albumin and globulin were not disturbed. Peters and van Slyke (1931) reported, however, that in chronic infection the plasma albumin concentration may be low, and one or two instances of low total protein are recorded in association with rheumatic fever and tuberculosis by Bing (1946) in his study of hypoproteinaemia. Grossman *et al.* (1945) in a series of patients with known negative nitrogen balance found normal levels for both total protein and plasma albumin. Wintrobe *et al.* (1947b) also stated, without giving evidence, that the albumin may be low.

Nitrogen Excretion.—A negative nitrogen balance develops in the presence of infection (Peters, 1944; Grossman *et al.*, 1945). Nitrogen excretion is very greatly increased in acute infections and to a considerable but less extent in chronic infections (Grossman *et al.*, 1945). The increased nitrogen is excreted in the urine in the form of urea and ammonia. Excretion of creatinine is unchanged. This loss of nitrogen is not definitely related to the febrile reaction (Grossman *et al.*, 1945) in acute infections; it may continue after the patient has become afebrile, and in certain chronic infections it may not continue in spite of continued fever.

Similar changes in blood chemistry are found in experimental animals after the production of a sterile abscess by turpentine injections (Cartwright *et al.*, 1946b). The significance of these metabolic changes in explaining the aetiology of the anaemia is discussed later.

Anaemia of Trauma

During the war observers investigating the blood picture of air-raid and battle casualties were struck by the fall in haemoglobin level that occurred after injury. It was repeatedly discussed, though with the exception of cases of severe burns it received little comment in the literature (Freebody, 1943-4; Vaughan *et al.*, 1946). A similar anaemia may occur after operative intervention which is not preceded by injury (Seaman and Ponder, 1943) and which, as in the cases studied, is not complicated by sepsis or treatment with sulphonamides; the latter often disturbs the picture of trauma. The available data on which to base a description of the anaemia are scanty—in our own series there were only 14 cases, and in none were blood volumes estimated. The picture, however, was similar to that seen in sepsis: a normocytic normochromic anaemia which in some instances became hypochromic and microcytic. This anaemia occurred even with slight trauma—for instance, in a man with a simple fracture of the patella.

During the period of falling haemoglobin the reticulocyte count is not raised, but during the period of regeneration there is a rise, often only within normal limits. In the few observations made on red-cell fragility it was not increased. Increased red-cell fragility has been described in the anaemia following severe burns (Shen and Ham, 1943), but it is possible that this results from actual injury to the red cells at the time of burning (Shen and Ham, 1943; Brown *et al.*, 1944). In such cases typical spherocytosis is found in the stained films.

Bone Marrow.—No quantitative or qualitative studies have been made of the bone marrow in anaemia associated with trauma.

Metabolic Characteristics

With the exception of nitrogen metabolism little is known of the metabolic characteristics of anaemia associated with trauma.

Serum Bilirubin.—In the few patients we studied the plasma bilirubin was normal (Vaughan *et al.*, 1946), though directly after the injury it tended to be higher than it was during the period of a rising haemoglobin.

There is no information about the level of the plasma iron or copper, the erythrocyte content of coproporphyrin, or the excretion of coproporphyrin. Observations on faecal urobilinogen are unconvincing (MacLagan, 1945).

Urinary Urobilinogen.—Though in studying air-raid and other civilian casualties quantitative examinations were not made, we were struck with the frequency with which we found considerable quantities of urobilinogen in the urine.

Nitrogen Excretion.—The negative nitrogen balance found in association with trauma is a striking and constant feature emphasized by many observers (Cuthbertson, 1935-6, 1944; Howard, 1945; Stevenson and Bensley, 1947). It occurs after injury or in post-operative conditions. It cannot be entirely prevented by giving high-protein diets, though it can be decreased in severity (Stevenson and Bensley, 1947). During the first ten days after injury nitrogen corresponding to more than 8% of the total body protein may be excreted (Himsworth, 1946-7). On a good diet with approximately 120 g. of protein and 3,000 total calories the average loss of nitrogen in a series of fracture cases was 225 g., or in terms of total protein 1,400 g. This negative balance lasted for an average of 35 days, reaching its maximum at about the sixth day. The recovery was slow. In a group of operative cases the same occurred, but the average loss was only 45 g. and the duration averaged nine days (Howard, 1945). The great difference from patient to patient is noticeable. The excretion is much less in those ill-nourished.

Blood Urea.—Immediately following injury there is a rise in blood urea, which falls to normal levels within the next few days (Vaughan, 1943; Taylor *et al.*, 1943).

Plasma Protein.—After injury, burns, or operative intervention there is often a fall in total plasma protein, but even in those cases in which the total plasma protein remains normal there is a fall in albumin, compensated by a rise in globulin and a rise in fibrinogen (Chanutin *et al.*, 1938; Taylor *et al.*, 1943; Elman, 1944; Croft and Peters, 1945; Vaughan *et al.*, 1946). This finding occurs after slight injury and is associated with only mild degrees of anaemia.

There are thus many striking points of similarity in the morphological and biochemical characteristics in the anaemia associated with sepsis, with sterile inflammatory abscesses produced experimentally, and with trauma. For instance, the anaemia is usually normochromic and normocytic, though it may become hypochromic and microcytic; there is no significant reticulocytosis; red-cell fragility is normal; and in all points on which evidence is available the striking changes noted in metabolism are similar (see Table).

Haemopoietic and Metabolic Findings in the Anaemia Associated with Sepsis and Trauma

	Sepsis	Trauma
Type of anaemia	Normochromic normocytic; hypochromic microcytic	Normochromic and normocytic
Reticulocytes	Raised after recovery from sepsis	Tend to rise with increasing Hb
Red-cell fragility	Normal	Normal (except some burns)
Bone marrow	Active	Unknown
Plasma proteins	Scanty data; low; albumin down?	Normal or low; albumin down; globulin up
Plasma bilirubin	Normal	Normal
Serum iron	Low	?
Serum copper	High	?
Erythrocyte coproporphyrin	"	?
Urinary and faecal coproporphyrin	"	?
Faecal urobilinogen	Normal	?
Urinary urobilinogen	May be high	May be high
Nitrogen excretion	Raised; negative balance	Raised; negative balance
Blood urea	Not known	Increased
Treatment	Transfusion; ? cobalt	Transfusion
Survival transfused cells ..	Normal	Normal?

Treatment

Iron and liver are in general ineffective in the treatment of either condition. There are certain cases of megalocytic hyperchromic anaemia in infants associated with sepsis

which are reported to respond to treatment with liver extract or folic acid. There are cases of hypochromic anaemia associated with both tuberculosis and "rheumatism" which respond to iron, but such cases are exceptional. Recent experimental results on animals suggest that cobalt is worthy of trial (Wintrobe *et al.*, 1947b). Cobalt has long been recognized as a haemopoietic factor in certain anaemias of sheep (Underwood and Filmer, 1935), and it has proved possible to produce experimental polycythemia in many experimental animals by administration of this metal. Wintrobe and his colleagues (1947b) found that rats which became anaemic after the formation of turpentine abscesses—a condition which appears in its metabolic findings to be comparable to infection—responded well to treatment with cobalt. The anaemia was cured though plasma protein and iron remained low. If cobalt was given simultaneously with the turpentine no anaemia developed. The significance of this finding is discussed later.

There is some evidence that a high-calorie high-protein diet may be of value in treating certain aspects of the disturbed biochemistry of trauma (Taylor *et al.*, 1943; Croft and Peters, 1945; Stevenson and Bensley, 1947). Howard (1945) and Stevenson and Bensley (1947) have shown that a high-protein high-calorie diet exerts some sparing action upon protein breakdown, but however much protein is given a negative balance cannot be prevented.

Transfusion of compatible whole blood is at present the only means of restoring haemoglobin and red-cell levels in both types of anaemia.

Aetiology of the Anaemia

What is the cause of this anaemia which is found clinically in association with either sepsis or trauma and which can be produced experimentally by sepsis, by trauma, and by sterile abscesses? It might be claimed that the anaemia of trauma was due to blood loss at the time of injury, but this alone is not sufficient to account for the fall of haemoglobin, though possibly it may be a contributory factor. For instance, the anaemia occurs after a slight injury such as fracture of the patella when there is no obvious blood loss, and it is progressive. Seaman and Ponder (1943) in a study of anaemia following operative intervention estimated the amount of blood lost by measuring the haemoglobin content of all swabs used and found that the fall in haemoglobin was greater than that accounted for by operative loss.

These three conditions have in common the breakdown of body tissues. It is tempting, therefore, to consider the possibility that the anaemia and accompanying metabolic disturbances are in some way dependent upon this common factor. Tissue breakdown is known to liberate many foreign substances, and one or more of these might exert a disturbing effect upon the erythron, causing aplasia, haemolysis, or dyserythropoiesis. On the other hand, the increased demand for tissue-building materials might result in a conditioned deficiency of haemopoietic factors and of other disturbances in metabolism.

It is justifiable to conclude that the anaemia is not dependent upon aplasia of the marrow, since such aplasia is not found, or upon haemolysis, since except in rare instances no destruction of red cells can be demonstrated. In these exceptional cases (Brown *et al.*, 1944; Mollison, 1947) the patient destroys not only his own red cells but also the transfused red cells from a healthy donor unduly fast. In the majority of cases there is no evidence of increased haemolysis. The serum bilirubin level is normal; there is no increased excretion of faecal urobilinogen

(Vaughan and Saifi, 1939), which is present invariably in haemolytic anaemias; and there is no increased detectable destruction of transfused healthy red cells (Brown *et al.*, 1944; Mollison, 1947). The increased urinary excretion of coproporphyrin III already noted (Vaughan and Saifi, 1939) might on theoretical grounds be derived from red-cell breakdown, since only coproporphyrin III is incorporated in the haemoglobin molecule, coproporphyrin I being probably a side-product in the formation of coproporphyrin III. Coproporphyrin III, however, is believed not to be found under any circumstances as a breakdown product of haemoglobin (Watson and Larson, 1947). In known haemolytic anaemias coproporphyrin I is recorded in excess, only in the urine (Watson, 1938). The amounts of coproporphyrin III found are also small and are not sufficient to account for the degree of anaemia. It would therefore appear more likely that a disturbance of synthesis at a later stage accounts for the increased excretion of coproporphyrin III (Dobriner *et al.*, 1937; Rimington, 1938).

Dyserythropoiesis, or faulty red-cell production, may be brought about by a variety of means, the commonest of which is a deficiency of haemopoietic factors. There clearly is no lack of the well-recognized haemopoietic factors, since they are ineffective in treatment. The response to cobalt of experimentally produced anaemia of sepsis in rats, mentioned above, suggests that a deficiency of cobalt may be of aetiological significance; further that there may be a conditioned deficiency of one or more amino-acids. Analysis of the facts concerning the metabolic disturbances present in this type of anaemia, details of which have already been given, points to a disturbance in the synthesis of haemoglobin which may prove to be due to such amino-acid deficiencies.

The stages in the synthesis of haemoglobin can be roughly shown as follows:

1. Precursor pyrrole substance $\begin{matrix} \nearrow \text{Copro I.} \\ \searrow \text{Copro III.} \end{matrix}$
2. Coproporphyrin III + iron $\longrightarrow$ haematin.
3. Haematin + globin $\longrightarrow$ haemoglobin.

Traces of both copper and cobalt may play a part in either stage 2 or 3.

In the anaemia under consideration there appears to be no failure in stage 1—the formation of coproporphyrin from a precursor—since there is an excess of coproporphyrin in the red cells (Cartwright *et al.*, 1946a). The evidence suggests rather that there is a failure in stage 2 (the junction of iron and coproporphyrin to form haematin), or in stage 3 (the junction of haematin and globulin).

What is known of stage 2? There is an excess of coproporphyrin III excreted in the urine, which may well be due to failure to complete the formation of haematin. There is a lack of iron in the circulating plasma, as shown by the persistent hypoferraemia which precedes the development of the anaemia (Cartwright *et al.*, 1946a). This hypoferraemia is *not* due to an actual lack of iron. Continuous infusion of iron sufficient to maintain a normal plasma iron is unable to bring about haemoglobin synthesis in the presence of infection (Greenberg *et al.*, 1947a). Wintrobe and his colleagues (1947a) by the use of radioactive iron found that iron administered intravenously to a pig with iron deficiency is readily taken up into the haemoglobin molecule, but in the presence of inflammation the uptake of iron to form haemoglobin is greatly decreased, though it returns rapidly to normal if the inflammatory process is checked. The iron is, however, taken up by the liver and spleen—the normal storage depots—in greatly increased quantities. No significant quantity is found in

the inflamed tissues (Greenberg *et al.*, 1947b). Iron is therefore not the limiting factor in the anaemia, though the diversion of iron from the plasma to the storage depots occurs. Wintrobe (1947b) suggested that this diversion is due to lack of cobalt, which they assume is essential to stage 2, the synthesis of haematin. In some way, therefore, not yet clear, the presence of infection necessitates the presence of abnormal amounts of cobalt for the synthesis of haematin. This is, however, extremely speculative. Cobalt might equally well be required in stage 3 of haemoglobin synthesis—namely, the junction of haematin and globin.

In dealing with the anaemia of trauma the hypothesis was advanced from a consideration of a different series of facts that possibly a failure of protein synthesis, presumably globulin, was responsible for this anaemia so affecting the third stage of haemoglobin synthesis (Vaughan *et al.*, 1946). We were impressed by the association of anaemia with a striking fall of albumin and rise of globulin in the plasma in patients without necessarily altering the total circulating protein. This change in relative protein levels is accompanied by greatly increased nitrogen excretion. How far it is related, if at all, to the remarkable changes in at least one proteolytic system of the blood—namely, that concerned with fibrinolysis—also occurring after injury is not yet clear (Macfarlane and Biggs, 1946; Biggs *et al.*, 1947). We must, however, include the anaemia of trauma and of sepsis among the many symptoms indicative of a wide disturbance of protein metabolism.

The cause of this disturbance is obscure. It may be due to disordered liver function following the action of tissue breakdown products—the presence of urobilinogen in the urine and the change in level of albumin and globulin so characteristic of this type of anaemia being also characteristic of liver disturbance. It may, however, be dependent upon a raiding of the protein stores of the body for some particular amino-acid required to restore injured tissues (Croft and Peters, 1945; Howard, 1945; Himsworth, 1946–7). In other words, after injury or infection the body suffers from a conditioned deficiency of some particular amino-acid. It is known, for instance, that both methionine (Glynn *et al.*, 1945) and lysine (Harris *et al.*, 1943) are essential for haemopoiesis. The effects on both the disturbed nitrogen balance and the anaemia of feeding these amino-acids (Croft and Peters, 1945) are at present conflicting.

Summary

It is suggested that the anaemia of trauma and sepsis is dependent upon a disturbance of haemoglobin synthesis affecting chiefly the globin element. This deficiency of globin is part of a wider disturbance of protein metabolism dependent upon the action of breakdown products liberated from the injured tissues or by the need of injured tissues for special amino-acids. Preliminary experimental observations suggest that possibly cobalt may be concerned at some point in this chain of events, but at present the importance of cobalt should not be exaggerated until its value in human cases has been confirmed.

From a practical point of view, apart from all theories as to the aetiology of the anaemia, it is important to treat patients with both trauma and sepsis on a high-protein diet, relieving the anaemia when severe with replacement therapy. It must be remembered, however, that it is not sufficient to provide a high-protein diet: the patient with sepsis or injury rarely feels hungry, and competent nursing care is essential in order to ensure that the necessary food is taken.

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The United Nations International Children's Emergency Fund held 14 meetings at Lake Success from Sept. 29 to Oct. 8, 1947. A survey has shown that at least 60 million children in Europe and the Far East need supplementary feeding and other help urgently. The organization now has sufficient funds to start some relief work, though more are still required. Shipments of dried milk, fats, and canned meats from the U.S.A. and Canada have already reached their European destinations.