clinical grounds, and there was only a 41% fall in the number of eosinophils; this is suggestive evidence of adrenal insufficiency, but enough time has not yet elapsed to enable the diagnosis in the case to be confirmed by a therapeutic test with D.C.A. In Case 17 there was no real evidence of adrenal insufficiency; yet the eosinophil count fell by only 25% after the administration of A.C.T.H.

While the diagnosis of Addison's disease may present no great problem in severe cases with classical pigmentation, hypotension, and crises, in a number of cases the blood pressure and blood chemistry are normal, pigmentation is atypical, and crises have not occurred. In the latter type of case the only clinical evidence for the diagnosis may be a combination of slight pigmentation, asthenia, and gastro-intestinal disturbance. Laboratory tests may be negative and there may be no calcification of the adrenal glands. The urinary 17-ketosteroid level may be reduced, but this is less helpful in the male in view of the testicular component. The Robinson–Power–Kepler test (1941) is perhaps the most helpful, but false positive results may be obtained in a number of conditions other than adrenal insufficiency (Levy *et al.*, 1946).

It is evident that there is still no single diagnostic test for Addison's disease which is completely reliable, and that, while a combination of the various tests may often be helpful, the diagnosis must in the last resort be made on clinical grounds.

Summary

The response of the eosinophil count and the uric-acid/creatinine ratio to the administration of A.C.T.H. was estimated in eight proved cases of Addison's disease, four cases of panhypopituitarism, and seven cases in which a diagnosis of adrenal insufficiency had been considered but not established.

Six of the eight patients with Addison's disease showed a fall of less than 50% in the eosinophil count. The other two showed falls of 57% and 75%, though in the former case the initial count was comparatively low and the change may not have been significant. Both these patients were suffering from a severe form of the disease, and the second of them died a fortnight after the test as a result of a severe respiratory infection; at necropsy no trace of adrenal cortical tissue could be found. In each of the four patients with hypopituitarism the eosinophil count fell by less than 50%. In the third group of cases four out of seven showed a normal eosinophil response; the other three showed subnormal responses, but one of them may prove to be a case of Addison's disease.

A number of workers have shown that the eosinophil count may fluctuate widely during the course of the day, and that the changes may exceed 50% of the initial level. Thus a fall in the eosinophil count exceeding 50% after the administration of A.C.T.H. does not exclude adrenal insufficiency, though a fall of less than 50% is strongly suggestive of such a diagnosis.

Changes in the uric-acid/creatinine ratio are of no value as an index of adrenal responsiveness.

The Thorn test is a useful addition to existing diagnostic methods, but it is subject to the limitations common to most laboratory tests, and the diagnosis must still, in the last resort, be made on clinical grounds.

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TOXIC REACTIONS DUE TO INTRAVENOUS IRON

BY

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The work of Nissim (1947) and Wilkinson and Slack (1949) on intravenous iron needs no introduction. Although its therapeutic value is undisputed, iron is nevertheless a dangerous drug. The dangers of its oral use, especially in children, are well known. That it can cause reactions intravenously is also becoming increasingly obvious. These are usually mild, but severe ones have been reported (Govan and Scott, 1949; Mooney, 1950; Slowik, 1950; Ramsey, 1950; Birch and Till, 1951). Two further cases are here recorded and discussed.

Case 1

A housewife aged 24 was admitted on November 22, 1950, with chronic pulmonary tuberculosis. This started in 1945, and had recently been complicated by amyloid disease manifested by massive albuminuria. On December 6 the haemoglobin was 40%, plasma proteins 7.2 g. (albumin 1.1 g., globulin 6.1 g.). A course of oral iron (tab. ferr. sulph. co.) was given, with poor response. On December 18 intravenous therapy was begun. "Ferrivenin," 100 mg. (5 ml.), was injected on December 18, 22, and 27. Within one minute of the last injection an epileptiform fit occurred, lasting four minutes. On recovering, the patient said her eyes became blurred after the injection, but she remembered nothing else. She afterwards complained of lumbar pain lasting 30 minutes, then pain in the chest for 24 hours.

On January 10, 1951, her haemoglobin was 72%. On February 9 a different preparation, "neo-ferrum," was used intravenously, 100 mg. (5 ml.) being injected slowly. A few seconds later she complained of a burning sensation at the

site of the injection, soon spreading to the head and neck, which flushed deeply. Shortly afterwards she complained of lumbar pain lasting a few minutes, followed again by a feeling of warmth and flushing. Some hours later she complained of pain in the left shoulder, heat, and sweating. Next day she was normal. On February 13 the haemoglobin was 76%, plasma proteins 7.3 g. (albumin 2.8 g., globulin 4.5 g.). There was still albuminuria. Later she had a three-stage thoracoplasty. Her haemoglobin was still 76%.

Case 2

A female hairdresser aged 24 was admitted on January 13, 1951, with acute tuberculous laryngitis and bronchopneumonia. There was a long history of "asthma." She was treated with "sterazol" and oral iron, and, although her tuberculous condition improved, her haemoglobin fell to 40%, plasma proteins being 7.5 g. Intravenous iron, using neo-ferrum, was therefore begun in mid-February; two doses of 100 mg. (5 ml.) were well tolerated. On March 2 a third dose of 100 mg. was given. Two minutes later she complained of severe pain in the head and thought she was dying. Severe dyspnoea and cyanosis supervened and the pulse became imperceptible. Adrenaline 1:1,000, 15 min. (0.9 ml.), was given immediately; five minutes later she felt better, although very "wheezy." Since admission she had complained of intermittent wheezy attacks relieved by ephedrine, adrenaline, and isoprenaline.

In view of the severe reactions, 1 dr. (3.5 ml.) of neo-ferrum thrice daily, orally, was substituted when the haemoglobin was 60%, with poor results. On April 4 it was decided to try intravenous therapy again, using very small doses of ferrivenin. On July 13 5 mg. (0.25 ml.) was given, but one and a half hours later she felt a slight constriction of the chest, which lasted all day. Further doses of 10 mg., 20 mg., and 40 mg. were given without ill effect. On July 23 80 mg. was given, and one hour later she went pale, then flushed, felt faint, and complained of tightness of the chest and dyspnoea, the whole lasting for a few minutes. Three further doses of 60 mg. were given without ill effect. On August 1 the haemoglobin was 63%. On August 3 70 mg. was given; this was followed one minute later by wheeziness and dyspnoea lasting two hours. On the 7th 65 mg. was followed in seven hours by faintness, and by pain in the limbs lasting 12 hours. Further doses of 62.5 mg. and 65 mg. were well tolerated. On August 14 67.5 mg. produced a slight wheeze after one minute, followed by faintness and headache for eight hours. Two further doses of 65 mg. were well tolerated, a third dose of 65 mg. being followed by a transient wheeziness and dyspnoea. A few further doses of 65 mg. were again tolerated.

On August 27 her haemoglobin was 70%. She now had had an eight-months course of sterazol with great clinical improvement in lungs and larynx. It was therefore stopped, and, although the possibility of drug haemolysis had been considered for some time, it was felt that, in view of her hopeless state on admission, both drugs should be persisted with. However, on November 27 oral iron was again substituted, and on December 12 her haemoglobin was 81%. During the whole period of treatment she still complained of intermittent wheezy attacks, relieved by adrenaline.

Discussion

The problem of intravenous iron intoxication may be approached in two ways: (1) the transport of iron in the blood; and (2) allergy. The intravenous method differs from the oral one in that the factors of local gastro-intestinal irritation and absorption are eliminated.

Transport of Iron in the Blood

Iron is directly introduced into the general circulation, and its attendant reactions must be intimately bound up with the question of transport in the blood itself. Laurell (1947) considers this to be closely associated with the binding capacity of the plasma proteins, especially the β-globulin-fraction iv-4(8) of Cohn *et al.* (1946). He introduced the term "saturation limit" for measuring the capacity of serum for firm binding of iron, including both the native iron content and that introduced therapeutically. Serum binds this iron content up to the saturation limit, which is not exceeded or influenced by the ingestion of large amounts of iron. The quotient manifest/latent iron-binding capacity of serum appears to vary regularly with changes in intermediary iron metabolism, and it seems probable that this iron-binding component of serum serves as a regulation of iron exchange between the various organs. After intravenous injection the value of serum iron is high, but in the presence of the normal saturation limit the latent iron-binding capacity is low. In chronic infection—for example, tuberculosis—however, the saturation limit is lowered too.

The unsaturated capacity of Cohn's globulin fraction to bind iron is roughly two to three times the normal level of serum iron (Klopper, 1951). Using rough calculations of plasma volume, he thinks that toxic effects arise only when the iron-binding capacity is exceeded in the individual injection. As Govan and Scott (1951) point out, reactions depend on the amount given in a single injection. In Case 2, although there appeared to be a critical level (65 mg. or more) above which a reaction was likely to occur, nevertheless a difference of as small an amount as 0.5 mg. between a reacting and a non-reacting dose seemed to be well tolerated. Klopper (1951) also thinks that complex saccharated iron compounds give up their molecular iron more slowly to the serum proteins than do simple iron salts. The rate of dissociation may well vary with the amount of globulin available at any given time. Case 2 was a known asthmatic. Altered tissue-protein relationships are well known to occur in this condition, but whether they can influence the amount of available globulin is conjectural.

The level of serum iron and the percentage saturation of iron-binding proteins are carefully regulated. Conditions in which the latter is increased include iron excess, bone-marrow block, and severe liver disease. The role of the liver is important because it is the chief iron-storage depot in the body. Depression of percentage saturation occurs in iron deficiency and in infections. Case 1 almost certainly had amyloid disease of the liver, and both cases were anaemic. Iron saturation and transport were therefore severely affected. Rath and Finch (1949) do not accept Laurell's hypothesis that the *degree* of saturation regulates iron absorption, for the injection of iron-binding protein exerts only a very temporary effect on the serum-iron level. It remains to be seen how much one may aid or interfere with iron transport by increasing or decreasing the amount of iron-binding protein.

It is well known that absorption of iron from the alimentary tract occurs by oxidation of the substance apoferritin to the crystallizable protein ferritin. In the blood stream the iron becomes detached from ferritin and is taken up by siderophillin, which may be the same as Cohn's globulin fraction, for transport. The rate at which ferritin releases its iron depends not on the level of serum iron but on the level of blood oxygen. Rapid transport therefore occurs only if the oxygen level is low, as in anaemia. If a similar method of take-up be postulated after intravenous therapy, the rate of take-up in both these patients who were severely anaemic may have been quickened. Andersson (1950), using rabbits, had to give 10 times the therapeutic dose before toxic reactions appeared. The factor of anaemia may explain the rapid onset of symptoms.

Allergy

The question of allergy seems to me to be important. Landsteiner (1924) showed, in guinea-pigs, that it is possible to make animals hypersensitive against a single chemical

group, such as *para*-arsanilic acid, by combining it with different proteins—for example, animals could be sensitized by injection of one azoprotein combined with diazotized *para*-arsanilic acid against another compound containing the same azo-component but a different protein. The animals did *not* react to compounds uncombined with protein. It would seem that the simple compounds mentioned are fixed by the cells in which the anaphylactic reaction occurs. This could be the mechanism causing the reactions to oral and intravenous iron, for, as has been discussed above, iron transport seems to depend on an iron–protein complex, and this protein component could well account for the anaphylactic phenomena such as were seen in Case 2—pallor, wheeziness, cough, and so on.

Sinclair and Duthie (1949) also describe a case in which 200 mg. caused flushing of the face and transient bronchospasm, but 100 mg. did not, nor did a further dose of 200 mg. In other words, by using graduated doses, one presumably gradually increases the amount of iron-binding protein used per injection. It is not the iron itself, therefore, but the protein complex which acts as a desensitizing agent (cf. pollen-allergy, etc.). Ramsey (1950) has described symptoms of nausea, vomiting, flushing, and shock after using single large doses of up to 900 mg. Some of these reactions occurred five hours after injection. He thought these late reactions resembled those due to cold haemoglobinuria, and that they were due to increased reticulo-endothelial activity. I feel that they resemble serum reactions—for example, antidiphtherial, antistreptococcal, etc. —and could be equally well ascribed to the same allergic causes. Although massive doses of antidiphtheria serum—for example, 100,000 units—can cause anaphylaxis, as little as 0.2 ml. of antiscarlatinal serum has also been responsible.

Beaumont and Dodds (1952) think that a long interval between injections predisposes to toxic phenomena, and quote the case of Govan and Scott (1949), in which a severe reaction with faintness, giddiness, vomiting, and slow pulse occurred, there being an interval of 12 days between the preceding and the toxic doses. I feel, however, that again this is more in keeping with an anaphylactic reaction.

Vaughan (1948) suggests that the anaemia of trauma and sepsis is dependent on a disturbance of haemoglobin synthesis, especially the globin element, this being, in turn, part of a wider disturbance of protein metabolism dependent on the action of breakdown products liberated from injured tissues or by the need of injured tissues for special amino-acids. In long-standing pulmonary tuberculosis, disturbance of protein metabolism occurs, as has been mentioned above. This special factor might well influence the tendency to iron reactions in tuberculous subjects.

Cartwright *et al.* (1946) showed that, in infection, iron injected intravenously was removed from the blood rapidly until the infection was controlled. Greenberg *et al.* (1947) also showed that major deviation occurred to the normal storage areas, especially the liver, because the iron cannot be used to form haemoglobin, the plasma excess being diverted as a protection against toxic effects. The use of large doses of intravenous iron, therefore, in subjects with chronic infective states such as tuberculosis may predispose to such effects, although the mechanism may be allergic, by flooding the circulation with unusable iron.

Case 2 is interesting in that this patient was a lifelong asthmatic. It will be recalled that, in the main, her reaction to intravenous iron in toxic doses was bronchospasm as characterized by wheezy dyspnoea. The factor of allergy in asthma is not disputed, neither is the ultimate cause of the symptoms—histamine release. However, the question whether the reactions in this case were due to iron or "asthma" is difficult to answer. Some evidence in favour of iron may be gathered from Ramsey (1950), who described a patient with tightness of the chest five hours after receiving 600 mg. Sinclair and Duthie (1949) also mentioned a case with bronchospasm occurring a few minutes after a dose of 200 mg. The question of dosage is relevant, in that in most recorded cases the provocative dose was 200 mg. or over. In Case 2, however, as little as 5 mg., or at other times 60 mg. and 100 mg., was necessary. It is well known that allergic subjects differ in their response at different times both to the specific allergen and to non-specific factors: for example, in hay-fever, exposure to pollen may or may not produce an intense attack of sneezing, as may rubbing the nose or injuring it in some way. Again, allergic symptoms are usually referable to the tissue most sensitive to the appropriate stimulus: for example, skin-allergy—itching, flushing, etc.; and bronchial allergy—wheezy dyspnoea, nose-sneezing, etc.

The essential cause of allergy and anaphylaxis is release of histamine, large amounts of which are present in lung and skin. This distribution may account for the flushing and bronchospasm seen in these cases. Histamine is, of course, normally found in the tissues, and immunization against it occurs from the formation of protein–histamine compounds. Its release is facilitated by trypsin and by injecting toxins, such as bee venom, staphylococcus, *Clostridium welchii*, etc. Most of the blood histamine is in the blood cells, and iron may well act as a release factor by allowing leakage to occur in some way from the blood cells into the plasma. The usual release method is by haemolysis. Case 2 was treated by sterazol (a sulphone compound), but the only evidence that could be ascribed to haemolysis was the persistently low haemoglobin level, despite continued iron therapy, followed by a fairly rapid rise to 81% on cessation of the drug.

Foster Kennedy (1951) stresses the importance of allergy in diseases of the central nervous system and believes that many phenomena—for example, migraine, epilepsy, encephalopathy—are due to local intracranial oedema, the result of allergy. Iron encephalopathy and headache could well be due to this cause. He thinks that inherited chemical patterns may determine the onset of allergy in any patient. This may well account for the tissue localization as well. Bearing on this is the opinion of Spencer (1951). From a study of ferrous sulphate poisoning in children he concluded that iron intoxication results in a widespread interference with cell function, especially in the brain, and that such central nervous system damage accounts for the symptomatology. This widespread interference could well be due to allergy—a widespread cellular upset with special emphasis on sensitized tissues.

The toxic effects of intravenous trivalent arsenicals such as neoarsphenamine bear some resemblance to those of intravenous iron. During or immediately after their injection vasomotor symptoms (also known as anaphylactoid and minor nitritoid symptoms), urticaria, and syncope occur. Following the injection, usually a few hours later, rigors, pyrexia, headache, pain in the back and limbs, vomiting, and diarrhoea also occur. Harrison (1942) thinks that these symptoms simulate anaphylaxis, and that all these compounds tend to damage capillary endothelium, with resultant petechiae in various organs, especially lung, liver, kidney, and brain. Tate (1948) also considers that arsenical dermatitis is an allergic phenomenon due to the interaction of an arsenic compound with epidermally fixed antibodies, although he acknowledges that Peters's experiments are more important. Peters (1950) has shown in classical experiments that the toxicity of arsenic depends on interference with the oxidizing enzyme pyruvate oxidase, which assists in the breakdown of glycogen to pyruvate. Dimercaprol forms a more stable ring compound with arsenic, thus regenerating the original enzyme. It has been shown that iron is intimately concerned in oxygen transport, but whether its toxicity is due to some similar act of competitive interference remains to be proved.

The nature of injected iron itself has been commented upon by many workers (Goetsch *et al.*, 1946; Ramsey, 1950; Klopper, 1951; Birch and Till, 1951). Goetsch *et al.* (1946) think that the effects may be due to a "heavy metal"

effect. Heavy metals produce pharmacological effects only when dissociated into ions of the metal or an oxide of the metal (E. M. Graham, 1951, personal communication). Spencer (1951) thinks that the free iron may combine with SH groupings and thereby interfere with oxidation. Klopper (1951), however, does not agree that toxic reactions are due to free iron. He compares the behaviour of iron to that of copper. If the latter is bound to the same protein molecule (which Klopper thinks is very likely), toxic reactions may be due to the appearance of copper selectively displaced from its protein substrate by its saturation with iron. Again, if the sulphydryl effect is the mode of action of iron-poisoning, then dimercaprol should be an effective antidote. Somers (1947), however, has shown that, in mice at any rate, dimercaprol increases the toxic effects of iron, whether used orally or intravenously.

Flocculation of the iron itself has been mentioned by Birch and Till (1951). Polson (1928) found that pulmonary embolism occurred on injection of dialysed iron. As described by Heath *et al.* (1932) and Nissim (1947), the chief reaction to intravenous colloidal ferric hydroxide is the precipitation of iron in the blood, leading to multiple emboli in the lungs and elsewhere. No such reaction has been ascribed to the widely used commercial preparations of to-day. Birch and Till (1951) stress that they used a "home-made" preparation.

The power of plasma globulin to bind iron is rapid but variable (Klopper, 1951). The question of a transient temporary concentration—for example, of *free* iron saccharate—in the plasma cannot be completely discounted. This transient effect could only account for immediate reactions, if at all, for it is unlikely that free iron would remain uncombined in the plasma after 6 to 12 hours. The occurrence of pain in the limbs and back might be accounted for by venospasm, the result of irritation by the free compound itself. Beaumont and Dodds (1952), however, think that impurities in the sugar used in the preparation may cause severe angina-like pains in the chest, arms, and back. They also think that rapid injection causes venospasm.

The question of the substrate itself acting as a toxic factor can, I feel, be discounted on the grounds that similar reactions have been described with different preparations, the only common factor being the iron itself.

Finally, Prain (1949) suggests that liver failure is the cause of death in iron poisoning, but the histological changes seem scarcely sufficient to account for this, for they are much less than in acute yellow atrophy. Death also occurs more quickly in iron poisoning than in liver atrophy. It would seem more likely that death is due to the widespread interference with cell function which undoubtedly occurs, whether this be caused by the iron itself or by anaphylaxis.

In conclusion, it must be conceded that the severity of iron reactions seems to depend on the dosage employed. The most severe reactions occurred with doses of 100 mg. or over. Wilkinson and Slack (1949) used 25 mg. of their original preparation of iron-sucrose as a starting dose, but Beaumont and Dodds (1952) use 50 mg. It would therefore be as well to employ doses of this order at the start if severe reactions are to be avoided.

Summary

The causation of iron intoxication is reviewed in the light of two further cases occurring in tuberculous patients.

From the work of Laurell, Klopper, and others it is concluded that an iron–protein complex is formed in the blood, the protein component being a globulin. Laurell's hypothesis of a saturation limit is further discussed in relation to the iron-binding capacity of the plasma proteins. This depends on several factors, including severe liver disease and severe infections.

The disturbance of protein metabolism occurring in liver disease and severe infections such as tuberculosis is suggested as being responsible in part for the occurrence of iron-reactions in these subjects.

Both patients were anaemic. Following Anderson's animal experiments, it is further suggested that anaemia may explain the rapidity of the onset of symptoms in these cases. The question of allergy is considered in relation to Landsteiner's work on drug allergy. The protein moiety of the iron–protein complex postulated above is suggested as being responsible for the allergic phenomena seen in the second case—pallor, wheeziness, and cough.

The severity of iron reactions in general would seem to depend on the dosage injected; the most severe reactions occurred after 100 mg. or more was given. The use of a small initial dose, say 25 to 50 mg., is stressed.

Graduated doses may act as desensitizing agents by presumably increasing the amount of iron-binding protein used per injection.

The essential cause of allergic symptoms—histamine release—is also considered in relation to the main toxic signs—flushing and bronchospasm. It is suggested that these occur because the largest amounts of histamine are present in the skin and lungs. The toxicity of iron is further compared with that of intravenous arsenic. An alternative hypothesis is put forward that iron acts, like arsenic, by competitive interference with an enzyme system. A sulphydryl effect is discounted on the grounds that dimercaprol *increases* the toxic effects of iron.

Finally, the cause of death is reviewed: the suggestion is put forward that death results from widespread interference with cell-function, probably due to an anaphylactic mechanism.

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