Heberden Society

Clinical Meeting, Nijmegen, The Netherlands, May, 1972

At a joint meeting of the Heberden Society and the Dutch Society of Rheumatologists, held at Nijmegen on May 12 and 13, 1972, the following papers were given.

Absorption and Retention of Iron in Rheumatoid Arthritis*

By J. WEBER, H. W. JULIUS, C. W. VERHOEF, and J. M. WERRE (*Municipal Hospital and Radiological Service Unit, Organization for Health Research TNO, Arnhem*)

The fraction of iron initially absorbed from an oral test dose, and the fraction retained in the organism after a few weeks, can be determined by means of a double tracer technique (Boender and Verloop, 1969). The question was studied whether, in patients with active rheumatoid arthritis and anaemia, an absorption and retention test could be used to differentiate between:

- (1) Patients with and patients without iron deficiency;
- (2) Patients who will and patients who will not show an increase in haemoglobin concentration after administration of therapeutic doses of iron.

Measurements were made, by whole-body counting, in 32 patients. The test dose contained 1 mg. iron, as ferrous sulphate. The results included:

- (1) A moderate correlation between retention and the estimated amount of iron in the reticulo-endothelial tissue of the bone marrow;
- (2) A higher correlation between the retention/absorption ratio and the bone marrow iron.

Furthermore, the correlation between the retention/absorption ratio and some other parameters appeared to be:

- (3) Very moderate for both the unsaturated and the total iron-binding capacity;
- (4) Low for changes in haemoglobin concentration after oral iron therapy;
- (5) None for changes in haemoglobin concentration after intramuscular iron therapy;
- (6) None for inflammatory activity indices.

These data suggest that determination of absorption and retention of iron in patients with rheumatoid arthritis and anaemia can contribute more to the diagnosis of (latent or manifest) iron deficiency than to the differentiation between, on the one hand, patients with rheumatoid arthritis and iron deficiency anaemia and, on the other hand, patients with rheumatoid arthritis and anaemia of different origin.

As compared with six iron-deficient patients without inflammation, nine patients with rheumatoid arthritis and bone marrow iron depletion showed a significantly lower mean value of absorption and retention. Both groups, however, retained virtually all the iron they absorbed.

*Study supported by grants from the Organization for Health Research T.N.O. and the Netherlands Rheumatism Association.

Discussion

DR. A. ST. J. DIXON (*Bath*) Are you absolutely sure that your rheumatoid arthritics were not taking something such as salicylates which might have interfered with the absorption of iron?

DR. WEBER We could not entirely exclude this, but all oral drugs were stopped the day before and on the day of the test. When receiving the dose of iron some patients were also taking phenylbutazone and some chloroquine or hydroxychloroquine. I do not know of any interaction between these drugs and iron absorption.

DR. J. K. VAN DER KORST (*Holland*) I am somewhat amazed by the homogeneity of your rheumatoid arthritis group. I always imagine that anaemia could be due to multiple causes, some people losing blood from the gastrointestinal tract and others having anaemia complicated by folic acid deficiency, and so on. Have you any comments on this?

DR. WEBER I think that there may be several causes of iron deficiency in these patients. Many of our patients with rheumatoid arthritis and iron deficiency suffered from loss of blood due to menorrhagia. There was also one patient who suffered from nose bleeding. We did not observe any patients with folic acid deficiency. Some had a low serum folate but I do not think this is a good measure of folic acid deficiency.

Reference

Boender, C. A., and Verloop, M.C. (1969) *Brit. J. Haemat.*, 17, 45

Kinetics of Iron Deposition in Rheumatoid Joints. By R. M. BENNETT, D. WILLIAMS, S. M. LEWIS, and P. J. L. HOLT (*Royal Postgraduate Medical School, London*)

Stainable iron is frequently found in the synovial membrane of rheumatoid joints. Senator and Muirden (1968) give an average value of 347 $\mu\text{g. iron/g. dry tissue}$ in rheumatoid patients, compared with 15.2 $\mu\text{g.}$ in normal controls. The derivation of this iron and its possible relationship to the anaemia of rheumatoid arthritis has attracted much speculation.

We have studied the rate of iron deposition in the synovial membrane of thirteen rheumatoid knees after giving an intravenous bolus of Fe^{59} -labelled transferrin with subsequent surface counting. Four osteoarthrotic knees were studied in a similar way for comparison.

It was found that the count rate over a rheumatoid knee shows a sharp fall over the first 24 h followed by a steady rise which parallels the incorporation of labelled iron into circulating red blood cells; the count rate over the knee representing the sum of the counts due to intravascular Fe^{59} and the synovial fluid/synovial membrane content of

Fe⁵⁹. Simultaneous counting over the thigh gives a count rate proportional to the intravascular component, which on subtraction from the knee count rate (after conversion to a common rate for Day 1) gives an 'accumulated knee' count—representing the intra-articular sequestration of iron—from which the daily sequestration of iron in the knee can be calculated.

The average accumulation of iron per day, per rheumatoid knee, was 1.25 mg. $\pm$ 2.38 (1 S.D.). Assuming this iron to be entirely derived from RBCs as a result of intra-articular bleeding, the average blood loss into a rheumatoid knee per day can be calculated to be 3.58 ml. $\pm$ 4.6 (1 S.D.).

Osteoarthrotic knees showed no significant accumulation of iron. There was no correlation between the degree of intra-articular iron deposition and the patient's haemoglobin, platelet count, or serum iron. It is concluded that synovial iron deposition in rheumatoid patients is unlikely to be a significant factor in the anaemia.

Discussion

DR. J. K. VAN DER KORST (*Holland*) Why do people with rheumatoid arthritis bleed in their knees?

DR. BENNETT We think the answer is due to a combination of increased vascularity of the synovium and the rough joint surface. When the joint surface is moved there is trauma to the synovium and bleeding occurs. I think we have shown very dramatically in one patient that bleeding occurred only when she was mobile.

DR. B. VERNON-ROBERTS (*London*) In one slide you showed iron being deposited in the subintimal synovial tissues, whereas in the late study there was good evidence of bleeding into the synovial cavity. In the patient that came to synovectomy, did you carry out autoradiography to determine the routes by which blood can pass from the synovial cavity into the deeper tissues?

DR. BENNETT We did, in fact, do this on several patients and obtained very convincing autoradiographs of iron in the subintimal layer of the synovium.

DR. J. A. MATHEWS (*London*) I never see blood in the fluid that I aspirate from the knee joints of patients that walk into the clinic. Can you explain this apparent discrepancy between my patients and your patient with a fistula?

DR. BENNETT I think it reflects remarkable powers of phagocytosis of the synovial membrane. Of course on microscopy, one can nearly always find blood in rheumatoid synovial fluids.

PROF. E. G. L. BYWATERS (*Taplow*) We have recently looked at some examples of pigmented villonodular synovitis where there is a very great accumulation of iron in the synovial membrane. In a number of these, on careful section of the whole synovial membrane, we have found evidence of localized haemangioma formation (Phillips, Ansell, Arden, and Bywaters 1971). I think that probably the presence of an increased number of blood vessels plus the ordinary trauma of walking accounts for this bleeding in pigmented villonodular synovitis and I think that this

could also account for bleeding of a lower degree in rheumatoid joints.

DR. P. FOWLER (*Macclesfield*) In some patients there was a very close correlation between the accumulation of iron in the right and left knees, whereas others showed wide differences. Could you correlate this in any way with clinical remission in the joints?

DR. BENNETT No, we could not. This was an interesting point; there was no correlation whatsoever between the clinical degree of inflammation and the amount of bleeding into the joint.

DR. J. WEBER (*Holland*) There is a controversy about whether iron and bleeding is harmful or an advantage for the joint. I would like to ask your opinion about this.

DR. BENNETT This is one of the unanswered questions that I put up at the end and I am really in no position to comment on it.

MR. A. R. TAYLOR (*Aylesbury*) I do a fair number of synovectomies and the fluid always appears remarkably clear to me. I think this explains why, in the shoulder joint, the fibrinous deposits are always bright yellow, whereas in the knee they have a brownish colour. This may be due to blood loss from the activity of the knee joint. In your case you have a persistent discharge after the removal of popliteal cysts and yet you have not undertaken synovectomy. Had you any conclusive proof that this was not an infected joint?

DR. BENNETT The interesting feature about this particular fistula was that the fluid was infected with *Staphylococcus aureus*, while the fluid from the joint cavity itself was completely sterile. This is in keeping with the concept of a one-way valvular mechanism between the joint cavity and Baker's cysts (Jayson and Dixon, 1970).

PROF. E. G. L. BYWATERS (*Taplow*) Regarding the relationship between bleeding into the joint and joint damage, very severe joint damage may occur in haemophilia and also, of course, in pigmented villonodular synovitis.

References

- Jayson, M. I. V., and Dixon, A. St. J. (1970) *Ann. rheum. Dis.*, 29, 415.
- Phillips, B., Ansell, B. M., Arden, G. P., and Bywaters, E. G. L. (1971) 'Abstracts of VII European Rheumatology Congress', Abstract no. 27.3. Arthritis and Rheumatism Council, London.
- Senator, G. B., and Muirden, K. D. (1968) *Ann. rheum. Dis.*, 27, 49.

Pain Threshold and Arthritis. By E. C. HUSKISSON and F. DUDLEY HART (*Westminster Hospital, London*)

Though there has been more speculation than experimentation, pain threshold has often been thought to influence the apparent severity of course of rheumatoid arthritis. It is of particular importance, that a high pain threshold could enable patients to carry on unsuitable work and therefore lead to destructive joint changes.

Using Keele's algometer (Keele, 1954), pain threshold was measured in three groups, patients with rheumatoid arthritis (106) or ankylosing spondylitis (50) and normal controls (50). The distribution of pain threshold was similar in normal subjects and patients with rheumatoid