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[1] Tchobroutsky G. Relation of diabetic control to the development of microvascular complications. *Diabetologia* 1978;**15**:143-52.
[2] Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and1973. *Diabetes Care* 1978;**1**:168-88, 252-63.
[3] Cohn L, Hingsom RA, Narduzzi JV, Seddom JM. Clinical experience with jet insulin injection in diabetes mellitus therapy: a clue to the pathogenesis of lipodystrophy. *Ala J Med Sci* 1974;**11**:265-73.
[4] Weller C, Linder M. Jet injection of insulin vv the syringe-and-needle method. *JAMA* 1966;**195**:156-9.

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Chlorthalidone-induced impotence

Impaired sexual function may occur with all classes of antihypertensive agents.[1 2] Thiazides are rarely incriminated,[3] however, and chlorthalidone has been implicated in only one, poorly documented case.[3] We therefore report five cases of sexual dysfunction that were associated with chlorthalidone. Four occurred in participants of the International Prospective Primary Prevention Study in Hypertension sponsored by CIBA. In this double-blind study patients are allocated at random to receive one or two tablets of either placebo or slow-release oxprenolol 160 mg daily. Additional antihypertensive agents except beta-blockers may be used, and we gave chlorthalidone when blood pressure was inadequately controlled.

Case reports

Case 1—A 56-year-old policeman with blood pressure 150/100 mm Hg and grade II hypertensive retinopathy was given one tablet of study medication daily. His blood pressure remained high and chlorthalidone 100 mg/day was added. Two months later he complained of severe impotence and decreased libido, which we attributed to oxprenolol, and the study medication was discontinued. When the code was opened, however, he was found to have been taking placebo. Chlorthalidone was then stopped, after which his sexual function improved.

Case 2—A 51-year-old clerk had been adequately treated with methyldopa, propranolol, and chlorothiazide, which he had discontinued for several months. Blood pressure was 200/115 mm Hg, with no evidence of organ disease. While taking chlorthalidone 100 mg and two tablets of study medication daily his blood pressure was 150/90 mm Hg. He complained of severe impotence, however, attributed to chlorthalidone. The diuretic was stopped and his sexual function improved. Six months later he had a myocardial infarction, and when the code was opened he was found to have been taking placebo. Subsequently his blood pressure was controlled by sodium restriction and sexual function was normal.

Case 3—A 58-year-old physician with blood pressure 160/105 mm Hg took chlorthalidone 100 mg and one tablet of study medication daily. He did not respond, and clonidine 0·15 mg/day was added, which lowered his blood pressure to 120/80 mm Hg. At the time he complained of decreased libido, which he attributed to chlorthalidone. The dose was therefore reduced to 50 mg/day and his sexual function improved. He volunteered for a new trial, and on two occasions on which the dose was raised to 100 mg/day sexual dysfunction promptly recurred. This was not improved by discontinuing clonidine.

Case 4—A 49-year-old farmer with blood pressure 170/110 mg Hg began treatment with chlorthalidone 50 mg/day, increasing to 100 mg/day. Three weeks later he complained of decreased libido and impotence and the drug was stopped. He then took one tablet of study medication daily, to which chlorthalidone 100 mg/day was added. Two weeks later he again complained of impotence, which subsided when the diuretic was stopped.

Case 5—This 62-year-old executive was not participating in the primary prevention study. He had formerly taken propranolol and chlorothiazide, which were stopped because of bradycardia. After several months of chlorthalidone 100 mg/day his blood pressure was normal but he developed severe impotence. Stopping chlorthalidone resulted in the return of sexual function, which remained normal with chlorothiazide 0·5 g and prazosin 4 mg daily.

Comment

In four of these patients sexual dysfunction occurred during treatment with chlorthalidone and either oxprenolol or placebo. In all five cases, however, sexual function improved on stopping or reducing chlorthalidone. In case 3 sexual dysfunction recurred twice on increasing the drug to 100 mg daily.

Two patients (cases 2 and 5) had taken chlorothiazide with no apparent adverse effect. This agrees with reports that some people may have sexual impairment from one drug known to have this effect yet tolerate another with the same propensity.[1]

Impotence from diuretics is rarely reported, possibly because patients and doctors are too embarrassed to discuss such problems. On the other hand, sexual impairment should not be attributed too readily to certain antihypertensive drugs, since impotence is more common in untreated hypertension than in normal people.[4] Hence in some hypertensive patients drugs may trigger impotence.

From our findings chlorthalidone-induced impotence may be more common than is generally supposed. Since the drug is often given with an antiadrenergic agent sexual complaints may be attributed to the sympatholytic drug. This may explain the paucity of other reports.

[1] Anonymous. Drugs and male sexual function. *Br Med J* 1979;ii:883-4.
[2] Bulpitt CJ, Dollery CT, Carne S. A symptom questionnaire for hypertensive patients. *J Chronic Dis* 1974;**27**:309-23.
[3] Anonymous. *Med Lett Drugs Ther* 1977;**19**:81-2.
[4] Bulpitt CJ, Dollery CT, Carne S. Change in symptoms of hypertensive patients after referral to hospital clinic. *Br Heart J* 1976;**38**:121-8.

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Unprecedented rise in incidence of infantile hypertrophic pyloric stenosis

The exact cause of infantile hypertrophic pyloric stenosis is not known but the condition probably occurs when genetically predisposed infants are exposed to a precipitating environmental factor. The incidence in the United Kingdom is widely quoted as two to three cases per thousand live births,[1] but fluctuations around these figures have been reported. The incidence in the Central Region of Scotland during the past 10 years rose dramatically from an average 2·1/1000 (1970-7) to 5·2/1000 in 1978 and 8·8/1000 in 1979. This last is the highest figure recorded in the world. I have analysed the 31 cases that occurred in 1979 to try to find a cause for this rise.

Methods and results

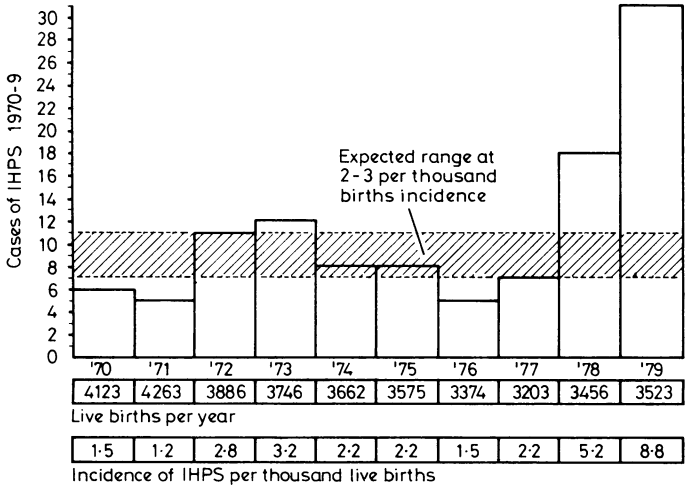
The Central Region of Scotland (population 271 810) is a well-circumscribed area, part rural, part industrial. It is served by Stirling and Falkirk district general hospitals, where virtually all deliveries occur and to which all paediatric hospital referrals are made. The paediatric department is run as a single unit. The senior staff did not change during the 10 years under review. Infants with hypertrophic pyloric stenosis are seen initially by the medical paediatricians, diagnosis is made by palpation of the pyloric tumour at a test feed, and a second opinion is sought before the infant is referred to the general surgeon. All cases included in this series were confirmed at operation.

The numbers of live births each year (figure) were taken from the hospital records and the region's statistics department, the figures agreeing to within 30 births for each year. The table shows the incidence of infantile hypertrophic pyloric stenosis during 1970-9. This differed significantly

through the decade ($\chi^2 = 57{\cdot}7$, df = 9, $p \ll\ll 0{\cdot}001$), mainly owing to the high incidences in 1978 and particularly 1979.

I analysed the 31 cases occurring in 1979 in more detail to see whether the expected associations had been distorted. The male to female ratio was 27:4 (6·8:1). Firstborn children constituted 42% of cases (13/31) compared with 31% of live-born children. The number of affected infants born each month, expressed as a percentage of births in that month, rose throughout the year, being lowest in February and highest in October. These findings agree with those of Dodge,[2] but the cases are too few to permit statistical analysis.

Information on stress in pregnancy was obtained by postal questionnaires from 27 mothers of affected infants and 17 control mothers taken at random from women whose infants were admitted to hospital in the first weeks of



Number of cases of infantile hypertrophic pyloric stenosis (IHPS) during 1970-9 and incidence per 1000 live births.

life with a serious acquired disorder during 1979. Questions on stress were based on those used by Revill and Dodge.[3] No significant difference was found between the two groups.

Information on drugs given to the mothers when pregnant and the affected infants was obtained from obstetric notes and from questionnaires sent to general practitioners and mothers of affected infants. The only drugs received by more than four of the 31 women were iron and vitamin preparations during pregnancy and promazine hydrochloride, pethidine, and nitrous oxide during labour. These have been used routinely in all women for many years. No one drug was received by more than three of the 31 infants, so that no drug can be implicated in causing the condition.

The addresses of affected infants were evenly distributed throughout the area in proportion to population density. The fathers of cases were in 20 different types of employment. Twenty-four general practitioners referred the 31 cases.

Comment

The incidence of infantile hypertrophic pyloric stenosis in the Central Region of Scotland was remarkably high in 1979. The cases show no divergence from the usual patterns of association of the disorder that might suggest a new factor in its aetiology. It will be interesting to find out whether the change in incidence is transient or permanent, local or national.

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[1] Carter CO, Evans KA. Inheritance of congenital pyloric stenosis. *J Med Genet* 1969;**6**:233-9.
[2] Dodge JA. Infantile hypertrophic pyloric stenosis in Belfast 1957-69. *Arch Dis Child* 1975;**50**:171-8.
[3] Revill SI, Dodge JA. Psychological determinants of infantile pyloric stenosis. *Arch Dis Child* 1978;**53**:66-8.

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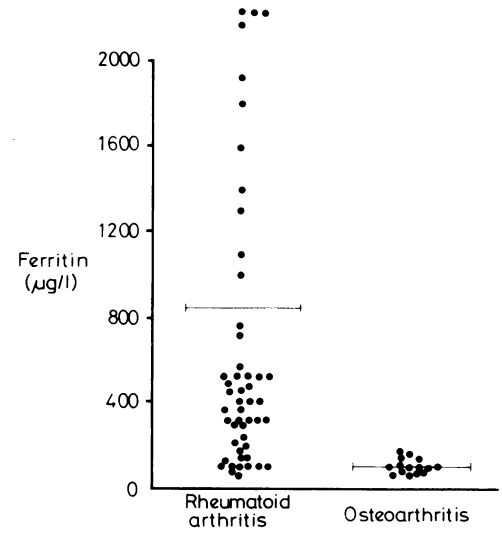
Synovial fluid ferritin in rheumatoid arthritis

In any inflammatory state a shift of iron occurs from the transferrin and red-cell compartments into reticuloendothelial cells.[1] In rheumatoid arthritis the inflamed synovial membrane shares many features of a reticuloendothelial organ[2] and the type A phagocytic cells contain abundant iron.[3] This iron is stored predominantly as intracellular ferritin, a water-soluble derivative of the protein apoferritin, potentially able to diffuse into synovial fluid. We therefore looked for ferritin within synovial fluid in an attempt to explore the relation between the inflamed synovium and the anaemia so prevalent in rheumatoid patients.

Patients, methods, and results

We studied 50 patients with rheumatoid arthritis and 15 with osteoarthrosis with associated effusion. Ferritin was measured in serum and synovial fluid by radioimmunoassay (Gammadab I^{125} ferritin kit; Travenol Lab). Ferritin was found in all synovial fluid samples. In patients with osteoarthrosis the concentrations were similar to serum concentrations, while in rheumatoid arthritis they were significantly higher ($p < 0{\cdot}0001$) and occasionally 20 times the corresponding serum value. The figure shows the distribution of fluid ferritin between the two groups; the difference is significant ($p < 0{\cdot}0001$). In patients with rheumatoid arthritis a significant correlation existed between serum ferritin and synovial fluid ferritin concentrations ($r = 0{\cdot}4$, $p < 0{\cdot}01$) and a negative correlation between synovial fluid ferritin and haemoglobin concentrations ($r = -0{\cdot}3$, $p < 0{\cdot}05$).



Concentrations of ferritin in synovial fluid in patients with rheumatoid arthritis and osteoarthritis.

Serum ferritin concentrations were not significantly different between the two groups, though both the highest and lowest values occurred in the patients with rheumatoid arthritis (mean ± SD 158 ± 241 μg/l in patients with rheumatoid arthritis and 104 ± 97 μg/l in those with osteoarthritis). No correlation was found between serum ferritin and haemoglobin concentrations.

Comment

The discovery of abundant ferritin within synovial fluid of patients with rheumatoid arthritis is of interest. It has been suggested that iron within the synovial membrane arises from the continued oozing of blood from the vascular granulation tissues into the synovial cavity, and that this may contribute appreciably to the anaemia of rheumatoid arthritis.[3]

Another hypothesis, which we favour, is that the synovial reticuloendothelial cells actively compete with other organs of the reticuloendothelial system for iron derived predominantly from effete circulating blood cells. This iron is stored as ferritin and the amount reflected by the synovial fluid ferritin concentration. The negative correlation between haemoglobin and synovial fluid ferritin concentrations might suggest that iron within the synovium contributes to the anaemia of rheumatoid arthritis. The significantly higher concentrations of ferritin in synovial fluid than serum, and the significant