PLASMA FIBRINOGEN IN RHEUMATIC FEVER

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In a study of indices of rheumatic activity, Ernstene (1930) investigated the fall in plasma fibrinogen concentration in 22 patients with rheumatic fever. He found that the mean fibrinogen concentration did not reach the normal value of 0.3 g. per 100 ml. until after about 12 weeks of intermittent salicylate therapy, and that there was pronounced individual variation in the rate of fall of plasma fibrinogen, so that the distribution of fibrinogen concentrations apparently became increasingly dispersed with the passage of time.

We have been studying the plasma fibrinogen concentration in rheumatic fever for some time, and since our experience, in 33 consecutive cases of acute rheumatic fever during the first 21 days of full salicylate therapy, differs from that of Ernstene (1930), our results are presented in this paper and their implications discussed.

Clinical Particulars and Methods

All the patients were febrile, and had a migrating polyarthritides with involvement of at least two joints when admitted to hospital. Patients with temperatures below

Plasma Fibrinogen Concentrations in Acute Rheumatic Fever Treated with Full Doses of Aspirin

Time	No. of Obs.	Range (g. per 100 ml.)	Mean Plasma Fibrinogen (g. per 100 ml.)	S.D.
On admission	33	0.49-1.15	0.78	0.14
4th day of aspirin therapy	32	0.40-1.02	0.64	0.14
7th " " " "	33	0.30-0.82	0.51	0.12
14th " " " "	32	0.24-0.63	0.39	0.10
21st " " " "	31	0.20-0.59	0.35	0.09
On discharge	33	0.20-0.41	0.30	0.05

100° F. (37.8° C.) or who complained of arthralgia unaccompanied by objective signs of arthritis were excluded, so that there was no doubt about the clinical diagnosis of acute rheumatic fever. Twenty-two were males and 11 females. Their ages ranged from 10 to 46 years; 26 were between 10 and 20 years.

Each patient was given full doses of aspirin to maintain the serum salicylate concentration between 30 and 45 mg. per 100 ml. Serum salicylate was estimated by Trinder's (1954) method, which we have found the simplest and most reliable for clinical use. The drug was given four-hourly, omitting one dose in the middle of the night, and actual doses ranged from 1 to 1.6 g. five times daily. In this way maximal doses were given without inducing serious side-effects.

Fibrinogen was estimated gravimetrically as fibrin, by the method of Foster and Whipple (1922), modified as follows: the fibrin was whipped on to a 30 s.w.g. stainless-steel wire held in a pin vice; the wire was trimmed and bent into a hook for drying and weighing on a 10-mg. capacity torsion balance.

Results

The plasma fibrinogen concentration before treatment was, in every patient, above the upper limit of normal,

taken as 0.4 g. per 100 ml. (see Table). It ranged from 0.49 to 1.15 g. per 100 ml. and the mean was 0.78 g. per 100 ml. During aspirin therapy the fibrinogen concentrations returned steadily to normal. By the 4th day, when polyarthritides had been relieved and fever had subsided, the mean value had fallen to 0.64 g.; on the 7th day it was 0.51 g.; on the 14th day 0.39 g.; and on the 21st day of intensive aspirin therapy 0.35 g. per 100 ml. At the time of discharge it was 0.3 g. per 100 ml., but this figure is not strictly comparable with the others because of the great variation of the duration of stay in hospital.

The frequency distribution of plasma fibrinogen concentrations (Fig. 1) during the first three weeks of aspirin treatment shows a remarkable uniformity in the return of the fibrinogen concentrations to normal. There is no evidence of progressively increasing variance. In terms of plasma fibrinogen concentration these cases form a homogeneous group during the first 21 days of full salicylate therapy. This is an unexpected result in a disease which, even with salicylate treatment, runs a notoriously variable course. It is particularly striking when compared with the great variation in rate of fall of plasma fibrinogen concentration found by Ernstene (1930),

FIG. 1.—Frequency distributions of plasma fibrinogen concentrations in acute rheumatic fever treated with aspirin, (a) on admission, (b) to (e) 4, 7, 14, and 21 days respectively after the start of treatment.

FIG. 2.—Plasma fibrinogen and serum salicylate concentrations in a case of rheumatic fever with relapses. —●—●— plasma fibrinogen, - - - ● - - - serum salicylate.

who used short intermittent courses of salicylate, in contrast to our continuous intensive and controlled therapy. In all other respects the two series are comparable, and, like Ernstene (1930), we had a small number of "polycyclic" cases which promptly relapsed after salicylate was discontinued. This happened in six of our patients, and each relapse was accompanied by elevation of the plasma fibrinogen, which reverted to normal after a second course of aspirin.

One of the patients developed a second similar relapse, and the findings are shown in Fig. 2, where it will be observed that discontinuation of salicylate was followed by clinical relapse and simultaneous elevation of plasma fibrinogen; these changes were immediately reversed when aspirin was started again. It is also noteworthy that in this case two parenteral courses of penicillin, in which 0.6 million units and 1.2 million units daily were started 12 and 7 days respectively before the first and second relapses, were not effective in preventing relapses.

Discussion

The plasma fibrinogen concentration in acute rheumatic fever treated with full doses of aspirin has been found to fall rapidly and uniformly in a series of 33 cases. Comparison of the present results with those of Ernstene (1930) emphasizes these features of our results: the mean plasma fibrinogen of his best, "monocyclic," subgroup did not reach 0.4 g. per 100 ml. till the fourth week of treatment; the corresponding time for *all* the present cases was two weeks. Even more striking in the present series is the lack of increasing scatter in the plasma fibrinogen concentration with the passage of time. This finding is difficult to reconcile with the view that salicylate only relieves the symptoms of rheumatic fever, and is impossible to interpret in relation to the careful study of Ernstene (1930) without inferring that an intensive and continuous course of salicylate does indeed, within three weeks, consistently lead to a rapid reduction in the plasma fibrinogen concentration in acute rheumatic fever.

Certain practical implications arise from the present study. Since hyperfibrinogenaemia is an essential feature of rheumatic fever (Fig. 1(a)), (1) the plasma fibrinogen concentration may be a reliable index of the course of the disease, and (2) sufficient salicylate, given for an adequate time, can restore the plasma fibrinogen to normal, and presumably arrest the rheumatic process, without necessarily influencing the chain of events leading to the elevation of the plasma fibrinogen concentration.

Above all, the present results provide definite evidence that salicylate does more than relieve symptoms. Even after 21 days' treatment seven of our cases showed fibrinogen levels which, although reduced, were still slightly abnormal; this confirms that there is no set optimum dosage schedule of the drug, and that in each case dosage and duration of therapy must be controlled not only by frequent serum salicylate estimations but also with reference to the fibrinogen concentration or some comparable index of rheumatic activity.

The connexion between plasma fibrinogen and the characteristic clinical and pathological features of rheumatic fever is being investigated further.

Summary

The abnormally high plasma fibrinogen concentrations found on admission to hospital in 33 patients with acute rheumatic fever fell rapidly and uniformly during a continuous intensive course of aspirin, controlled by serum salicylate estimations. This clearly demonstrates the advantage of proper aspirin therapy.

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SUPERFICIAL MALIGNANT LESIONS OF BLADDER TREATED BY RADIOACTIVE COLLOIDAL GOLD (^{198}Au)

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In the treatment of multiple superficial lesions of the bladder intracavitary irradiation has a distinct advantage over external deep x-ray therapy because it protects adjacent healthy organs. Several techniques have been developed for the use of gamma-radiation-emitting radioactive substances as an intravesical source of irradiation (Friedman and Lewis, 1949; Becker and Scheer, 1952; Schulte, Hinman, and Low-Beer, 1952; Walton and Sinclair, 1952). The disadvantage of penetrating gamma-radiation, however, is the development of secondary cystitis and a risk of fibrosis with impaired function of the bladder.

For very superficial lesions it seemed possible to use beta-radiation. Because the dose of beta-emission falls rapidly at depth the best method is the instillation of a radioactive solution direct into the bladder in order to get the emitting substance into close contact with the bladder mucosa and to surround the papillomatous villi by the radioactive material. Ellis and Oliver (1955) used radioactive gold (^{198}Au) in this way. Einhorn, Larsson, and Ragnhult (1955) suggest the use of radioactive yttrium (^{90}Y), and Walinder (1955) colloidal $^{76}\text{As}_2\text{S}_3$ for the purpose.

Radioactive colloidal gold is suitable for this method because of its half-life, its type of emission, and its colloidal nature. Since the half-life is short (2.7 days), there will be no danger of contamination after a few days. It emits about 95% of beta-radiation with 0.96 MeV energy, and 5% of gamma-radiation with 0.41 MeV energy. The maximal penetration of its beta-particles in soft tissue is about 3.8 mm., and of the half-value layer about 0.3 mm. Thus its maximum effect is confined to the bladder epithelium, leaving the sub-epithelial tissue almost unirradiated. Its colloidal nature protects against its resorption.

This preliminary report is based on our experience with radioactive colloidal gold (^{198}Au) in the treatment of superficial malignant lesions of the bladder since May, 1955. Our material included papillary cancer and also recurring extensive papillomata without histological cancer. Three cases are here briefly reported.

Methods

The radioactive material was obtained from Harwell. After the decision to use the colloidal gold method, fluid intake was restricted on the day prior to treatment and forbidden on the day of treatment. When the activity in millicuries per millilitre had been determined, the desired dose in millicuries was drawn into the lead-shielded syringe and introduced into the bladder through an ordinary bladder catheter. Injection was readily accomplished after removal of urine by catheter. Sterile isotonic saline solution was used for rinses. At an appropriate time the contents of the bladder were run off, and the bladder was washed out with a warm solution. The volume of the removed fluid was measured for dose calculation. With suitable precautions the personnel received no hazardous amounts of radiation.