presentation. Bailey et al also reported slight leucopenia and raised ESR in their patient, and abnormal liver-function tests were a presenting feature. The association with *Y enterocolitica* has been noted in three other patients.[2] However, the cause of Kikuchi's disease is uncertain.

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FLUOR: ANOTHER CARDINAL SIGN OF INFLAMMATION

SIR,—"*Notae vero inflammationis sunt quattuor: rubor et tumor cum calore et dolore*".[1] When we speak of the cardinal signs of inflammation—rubor, calor, tumor, dolor—we consistently omit one that is obvious to all our patients. The common cold leads to a runny nose, gut infection to diarrhoea, and bronchial injury to increased mucus secretion. Obvious examples also accompany inflammation in the vicinity of other exocrine glands, such as the lacrimal gland. Essentially all these are increased secretion—*fluor* in Latin.

The biological significance of the increased flow seen in inflammation is not trivial. Every medical student is taught that the normal flow of the contents of hollow organs can be a defence against infection. A basic principle of pathology is that "obstruction of a hollow organ leads to infection behind the obstruction". Often quoted examples include infection behind carcinoma of the colon or bronchus and following obstruction of the urinary or biliary tracts. As far as the host is concerned, fluor must presumably greatly assist the evacuation of any causative agent. From the point of view of some microbes, it enhances communicability, such as by droplet transmission of respiratory infections or the faecal-oral route. Like other so-called defence mechanisms, it can also do harm to the host. A substantial element of the morbidity and mortality of chronic bronchitis and especially asthma is attributable to the excessive secretion of mucus associated with inflammation of the bronchial wall. Diarrhoea can produce dangerous dehydration.

So far as I know, the mechanism of fluor has not been studied specifically, although Florey[2] made thoughtful contributions to the mechanisms of increased mucus secretion. It might be the result of one or more of the chemical mediators of inflammation, or simply the locally increased blood flow. Perhaps if we recognise it for what it is—a common and important general reaction to injury—it may merit some investigation.

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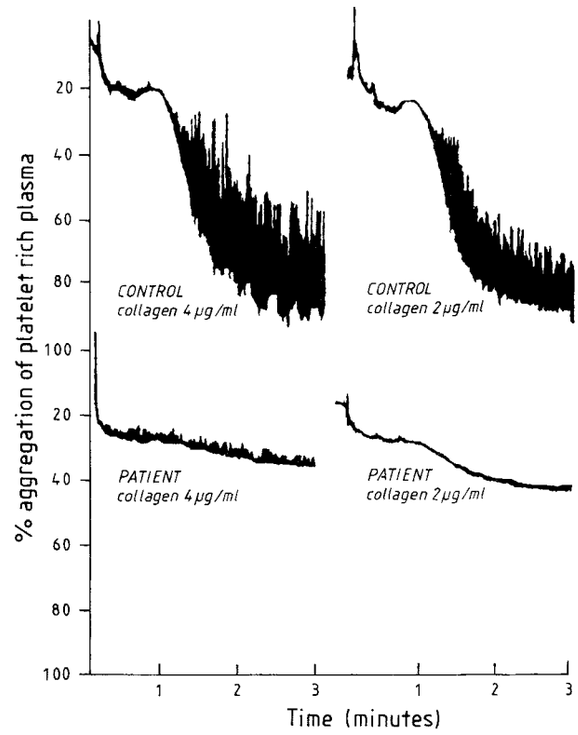
SPONTANEOUS NON-GASTROINTESTINAL BLEEDING ASSOCIATED WITH DICLOFENAC

SIR,—Haematemesis and malaena are well-recognised complications of non-steroidal anti-inflammatory drugs. Leucopenia, thrombocytopenia, and aplastic anaemia have also been described.[1] Defects in platelet aggregation are thought to result from inhibition of cyclo-oxygenase, and hence production of thromboxanes which are potent platelet aggregators.[2] Despite this well-recognised occurrence, bleeding outside the gastrointestinal tract is uncommon. Indeed, we are aware of only one such case.[3]

A spontaneous haematoma developed in a 73-year-old white female, who had been taking diclofenac 100 mg daily for two years.



Platelet aggregation curves in control (top tracing) and patient while taking diclofenac (lower tracing).

There was no history of gastrointestinal haemorrhage, epistaxis, or other bleeding manifestations. She gave no family history of haemorrhagic disorder, and had not had excessive bleeding during or after dental extraction or surgical procedures. The only other drug she had taken was bendrofluazide for mild hypertension. She had a haematoma measuring 22 x 16 cm in the upper outer aspect of the left thigh. Bleeding time, haemoglobin, white cell count, platelet count, international normalised ratio, and partial thromboplastin time were normal. Platelet aggregation with ADP 1, 3, and 5 mmol/ml, and ristocetin 1·2 mg/ml was normal, but was strikingly reduced with collagen 2 and 4 mg/ml (figure). The patient was asked to discontinue diclofenac but continued taking bendrofluazide.

Platelet aggregation with all these agents returned to normal. After reintroduction of the drug three weeks later the abnormal platelet aggregation curves with both concentrations of collagen were reproduced. The patient was again asked to discontinue the drug in view of her forthcoming knee replacement.

Diclofenac is a widely used anti-inflammatory analgesic. Since it inhibits prostaglandin synthetase it is used as an anti-platelet drug. Francis et al[2] reported reduced platelet aggregation to the low concentration of collagen with short courses of diclofenac, which they attributed to its inhibition of arachidonic acid synthesis. Our patient took the drug for a long period and the effect on platelet aggregation was seen with both high and low concentrations of collagen. Collagen induces secondary platelet aggregation by activation of the prostaglandin/thromboxane system and by ADP release. Our findings suggest that it not only inhibits arachidonic acid/thromboxane synthesis, but also the ADP release reaction, and that its effect is time dependent. This report has wide implications since it confirms diclofenac's potent anti-platelet effect. Its use preoperatively is potentially hazardous. Indeed, Francis et al[2] reported significantly greater wound drainage and postoperative falls in haemoglobin in patients taking diclofenac. We recommend that diclofenac is stopped 10–14 days before open surgery is undertaken.

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