performance was so deficient as to suggest a specific developmental failure. Fourteen of these children were matched for age, sex, handedness, verbal I.Q., and home and school background with an equal number of children drawn from the same sample who had shown no evidence of selective visuo-motor impairment. Both groups were followed up for a three-year period.

The children with visuo-motor defect were found to be significantly inferior to the controls on a series of tests of spatial judgement and manual skill, to present a variety of educational problems, especially in regard to spelling and arithmetic, and to give evidence of a relatively high incidence of maladjustment. There was also evidence of a relatively high incidence of perinatal abnormality in this group, raising the possibility of minimal early brain damage.

This study supports the contention that agnosic-apraxic disabilities in otherwise normal children are by no means rare and warrant wider recognition.

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Effect of Salicylates in Urticaria

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The ingestion of aspirin often seems to be responsible for attacks of urticaria and it has been assumed that there is an immunological basis for this effect. However, in the past few years it has been realized that in some patients with chronic urticaria which is apparently unrelated to food or drug allergy an exacerbation may be caused by taking aspirin (Calnan, 1957; Warin, 1960). The purpose of this investigation was to determine the incidence of this phenomenon and whether there are any clinical differences between patients with chronic urticaria who react in this way to aspirin and those who do not. In addition, we wished to discover which part of the aspirin molecule was responsible and whether the effect extends to the physical urticarias and weals induced by intradermal injections of histamine.

Subjects and Methods Used

Patients included in the study were drawn from those routinely seen in the outpatient department at the Bristol General Hospital. Others were referred to us by colleagues and in answer to a circular sent to general practitioners in the area. For the purpose of this study we have defined chronic urticaria as urticaria without an obvious cause which had been present for at least six weeks. All the patients had dermal weals, most of them also had attacks of angioedema. A few who presented with angioedema had had at some time a phase of dermal wealing. A total of 228 patients have been studied. The proportion of males to females was 1 : 1.7, and ages ranged from 3 to 71 years.

As part of a detailed interview patients were questioned regarding the ingestion of aspirin or aspirin-containing compounds, and any association with an increase in weals. If there was any possibility of exacerbations from this cause an aspirin test was carried out. This was done on a patient-blind basis, and consisted of control inert tablets identical in size, colour, and taste to aspirin labelled "A" and aspirin tablets labelled "B." The inert tablet was always taken first, as it was felt that if the patients were given the aspirin first and reacted badly to it they would be reluctant to take the second tablet and so invalidate the test. A and B tablets were taken on consecutive days, the dose varying according to the history. Thus if the history were suggestive of an aspirin reaction the initial dose was 300 mg., whereas if the history were less certain it was 600 mg. of aspirin. Any change in the skin and the timing of such a change was noted by the patient. In eight patients the provocation tests were repeated with increasing doses of aspirin. In 21 of the patients who reacted to the test doses these were repeated with sodium salicylate (18 patients) and phenyl salicylate (3 patients) in equivalent molecular doses.

In order to assess the effect on physical urticaria 10 patients with dermographism, five with cholinergic urticaria, and three with cold urticaria were studied. Measurements in all cases were carried out four hours after administration of an inert tablet and later aspirin (300 or 600 mg.). In the dermographic patients a standard method of measurement of the wealing tendency was evolved. A spring-loaded blunt-ended projection which could give known pressure effects of 60, 120, 180, and 240 g. was applied to the volar surface of the forearms in a 3–4 cm. line through a piece of thin metal, cut to admit the projecting point. The width of the weals was measured direct after seven minutes and a graded response to the different pressures obtained. Patients with cholinergic urticaria were exercised for 10 minutes and the amount of wealing was assessed clinically by the patient and the observer. In cold urticaria the size of the weal produced by contact with ice for 10 minutes was difficult to measure and was again assessed clinically. Four patients with urticaria pigmentosa were also studied and weals measured with the same method as used in the dermographic patients before and after aspirin.

In a group of 14 patients comprising four who had reacted to the aspirin test and 10 who had not, the effect of aspirin on induced histamine wealing was decided by measuring the weals produced by intradermal injections of

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0.05 ml. of 0.0001%, 0.001%, and 0.01% histamine acid phosphate solution on two separate occasions—the first four hours after the control tablets and the second four hours after 600 mg. of aspirin. Weals were measured by first taking a tracing of the weal and then transferring this to millimetre graph paper. An accurate measurement of surface area could be calculated by counting the squares in the outline of the weal.

Results

Out of the 228 patients with chronic urticaria, from the history, there appeared to be a possibility of an exacerbation caused by taking an aspirin-containing compound in 112, and in these the provocative test was carried out. There was no response in any case to the inert tablet, but 50 patients reacted to aspirin. This was usually felt within four hours. Pruritus, often of the lips and eyes, was the first symptom, and was followed by the development of widespread weals, and in many cases swelling of the lips and eyelids. The attack settled in a time varying from a few hours up to four to five days, but a few patients noted that the worsening from one dose of aspirin lasted for several weeks. It was thus shown that aspirin had an exacerbating effect in at least 22% of all the patients with chronic urticaria.

Of the eight patients tested with increasing doses of aspirin, four failed to react at all to 300 mg. of aspirin and had successively worse reactions with 600 and 1,200 mg. In four others the reaction worsened so markedly between 300 and 600 mg. of aspirin that a third dose was not given.

Furthermore, this quantitative effect was supported by clinical observations in other patients who commonly reported that they had taken a single aspirin without effect, but on occasion had ingested a larger dose over a short period—for example, two tablets (600 mg.) four times a day for two days—with the result that their urticaria became worse.

Of the 21 aspirin reactors on whom provocative tests were performed with compounds chemically related to aspirin, 13 out of 18 suffered worsening of their urticaria after sodium salicylate and two out of three after phenyl salicylate.

In the 10 patients with dermographism the measurement of the weal width was in no case greater after aspirin than after the inert tablets. The weal size in the four cases of cold urticaria did not appear to be larger after aspirin. The five patients with cholinergic urticaria also showed the same degree of wealing after exercise with both the aspirin and inert tablets. Thus no effect of aspirin on these physical urticarias was demonstrated. The four cases of urticaria pigmentosa showed no increase in the width of weal after aspirin as compared with the inert tablets, and none had any general reaction to it.

The 14 patients in whom the effect of aspirin on induced histamine wealing was assessed can be divided into two groups; the first comprising 10 who had not reacted to the test dose of aspirin and in whom the histamine weal size was not different before and after aspirin, and the second comprising four who had reacted to aspirin, in whom the histamine weals were significantly larger after aspirin (Tables I and II). Table I shows the weal size in both groups four hours after ingestion of inert tablets. There is no statistical difference between the two sets of figures. Table II shows the same measurement four hours after taking 600 mg. of aspirin. The weal surface area in the four patients who had reacted to aspirin is obviously much greater—($P=0.001$). The reaction to 0.05 ml. of 0.0001% histamine acid phosphate solution was such in all four patients that intradermal tests with higher concentrations of histamine were not attempted.

TABLE I.—*Weal Surface Area Measured Four Hours After Ingestion of Inert Tablets*

0·05 ml. Histamine Acid Phosphate Solution Intradermally	Non-reactors (10 Patients)		Reactors (4 Patients)	
	Actual Areas (sq. mm.)	Mean (S.E.)	Actual Areas (sq. mm.)	Mean (S.E.)
0·0001%	59, 62, 65, 68, 70, 70, 71, 71, 71, 71	68 (±1·5)	68, 69, 72, 75	71 (±1·6)
0·001%	185, 188, 189, 192, 195, 198, 200, 200, 201, 202	195 (±1·9)	195, 199, 201, 209	201 (±2·9)
0·01%	274, 276, 278, 280, 281, 283, 285, 288, 292, 293	284 (±2·0)	284, 289, 296, 307	294 (±5·0)

TABLE II.—*Weal Surface Area Measured Four Hours After Ingestion of 600 mg. of Aspirin*

0·05 ml. Histamine Acid Phosphate Solution Intradermally	Non-reactors (10 Patients)		Reactors (4 Patients)	
	Actual Areas (sq. mm.)	Mean (S.E.)	Actual Areas (sq. mm.)	Mean (S.E.)
0·0001%	67, 69, 70, 73, 75, 75, 76, 77, 79, 80	74 (±1·4)	275, 281, 288, 296	285 (±4·5)
0·001%	173, 177, 181, 184, 186, 186, 187, 189, 193, 194	185 (±2·1)		
0·01%	285, 286, 288, 292, 295, 301, 305, 306, 306, 306	297 (±2·8)		

Further clinical observations of the series of patients revealed points of interest. Firstly, there would appear to be no clinical difference or variation in the pattern of urticaria between those patients who react to aspirin and those who do not. There was evidence that the effect of aspirin becomes apparent in a susceptible individual only when several factors are acting at the same time. Patients often mentioned that a head cold, sore throat, gastrointestinal upset, period of anxiety, plus taking a large dose of aspirin exacerbated their urticaria.

The urticarial tendency in patients with chronic urticaria fluctuates in degree, and the severity of an aspirin-induced exacerbation is greater when the wealing tendency is pronounced. Thus patients who have shown a reaction with 300 mg. of aspirin, at a later stage when the wealing tendency was less have had little or no reaction with 600 mg., and in some patients tested when the urticaria had cleared an aspirin effect has been obtained only when doses up to 2,400 mg. of aspirin have been given.

Another interesting clinical association was that of the 50 patients who developed an exacerbation after aspirin four also had exacerbations after both penicillin and antitetanus serum on different occasions.

The series include four families in which successive generations have suffered from chronic urticaria and exacerbations due to aspirin. In one, the mother, who had suffered from chronic urticaria for 17 years, was shown to react to aspirin and sodium salicylate. One of her sons has had urticaria for nine years and is also an aspirin reactor. In one of our youngest patients, aged 4, who has had urticaria since the age of 18 months, wealing is increased after aspirin and also penicillin; her mother and one maternal aunt suffer from chronic urticaria which is severely increased after taking aspirin.

Discussion

It is difficult to understand the mechanism of this weal-exacerbating effect of aspirin in 22% of patients with chronic urticaria. A nonspecific histamine-liberating effect has been suggested, and Hamrin (1957) described a case of a patient with urticaria pigmentosa who developed flushing, vomiting, and collapse after aspirin, and it was considered that this result was due to histamine release. However, we have been unable to repeat these observations in the four patients with urticaria

pigmentosa, and, moreover, on pharmacological grounds it would be unlikely for aspirin, an acid substance, to have such an action, as most recognized histamine liberators are bases.

Another possibility would be that aspirin was acting as a hapten, forming an antigen when combined with serum proteins. We have no clear evidence against this, but we would have to assume that at least one in five patients who suffered from chronic urticaria would also have such an allergy to aspirin.

That aspirin in some way renders the skin in these patients more sensitive to histamine is suggested by the present report that intradermal histamine weals were larger after aspirin in these patients. In this connexion it is interesting that Juhlin and Rune (1962) have reported that the threshold to 48/80, a known histamine liberator, is lowered in acute urticaria.

It has been stated in the past that aspirin sensitivity is specific to acetylsalicylic acid and does not extend to related compounds. In the present investigations similar reactions were obtained in most patients from sodium salicylate and phenyl salicylate, and it would seem likely that it is the salicylic acid radical which is responsible for aspirin reactivity.

Whatever the underlying cause, it is now established that a point of great practical importance in the management of patients with urticaria is to avoid any administration of salicylates.

The investigation of a patient with chronic urticaria, aspirin reactivity, and jaundice revealed abnormal liver histology described as atypical portal cirrhosis. This finding prompted the investigation of all patients who reacted to aspirin. To date, two other similar cases have been found. It is intended to report later the details of these three cases with the triad of chronic urticaria, aspirin reactivity, and liver disease.

Summary

Aspirin-containing drugs will cause exacerbation in some patients with chronic urticaria. In 112 out of 228 patients with chronic urticaria such a reaction could not be excluded from the history, and provocative test doses of aspirin were given; 50 patients (22%) developed a well-marked increase in the urticaria. No clinical differences could be observed between the patients who reacted in this way and those who did not.

This action of aspirin is probably due to the salicylic acid radical, as most patients tested have had similar reactions with doses of sodium salicylate and phenyl salicylate.

It has been shown in eight patients that the increase in wealing is proportional to the dose of aspirin administered. In four patients who did not react at all to 300 mg. of aspirin there were successively more severe reactions to 600 and 1,200 mg. In four others the reaction increased so much between 300 and 600 mg. that a larger dose was not given. The quantitative effect is further supported by the clinical observation that some patients have developed exacerbations when large doses of aspirin have been taken and have shown no reaction to isolated small doses.

With appropriate measurements, before and after aspirin, it has been shown that there was no effect on the physical urticarias, including 10 patients with dermographism, five with exertion urticaria (cholinergic), and three with cold urticaria. Similarly, no effect was demonstrated in the wealing in four patients with urticaria pigmentosa.

It has been demonstrated that induced intradermal histamine weals measured four hours after 600 mg. of aspirin were larger in a group of patients who had reacted to aspirin than in a control group. It is suggested that the mode of action of aspirin in chronic urticaria is by enhancing the effect of histamine in the skin.

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Clinical Measurement of the Anti-inflammatory Effects of Salicylates in Rheumatoid Arthritis

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Salicylates in relatively low dosage modify certain components of the inflammatory reaction in animal experiments (Adams and Cobb, 1963). Theoretically they may be used in rheumatoid arthritis to promote the relief of pain or for their anti-inflammatory effect. It is important to determine whether there is a different dose-response relationship for each of these characteristics.

The cardinal signs of inflammation—pain, heat, redness, and swelling—are the indices available for the direct clinical assessment of inflammatory activity in rheumatoid arthritis. Pain is subjective and difficult to quantitate. Joint heat was studied by Smyth and Clark (1957) and by Vaughn, Howell, and Kiem (1959); it was found to be of little value. The latter authors also found redness an unsatisfactory index for assessment. Hart and Clark (1951) introduced the method of standard jewellers' rings for the measurement of joint size, by which accurate serial recordings could be made.

Fremont-Smith and Bayles (1965) investigated the effect of high dosage of salicylate in 11 patients in hospital with rheumatoid arthritis. Aspirin was given orally in increasing quantity over a five-day period until the largest tolerated dose was reached—on average, 5.2 g./24 hours. In most cases dosage increase was stopped because of tinnitus or deafness. Potent analgesics without anti-inflammatory action were then abruptly substituted. An increase in joint size, measured by standard jewellers' rings, and deterioration of grip strength, symptoms, and other indices followed rapidly the withdrawal of aspirin. They concluded that all patients with active rheumatoid arthritis, whether it was mild or severe, should receive salicylates regularly in the largest tolerated dosage in the absence of obvious contraindications. Because of side-effects "blind" techniques and quantitation of the changes were not attempted.

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