

How far treatment with synthetic folic acid may be successful in other forms of macrocytic anæmia remains to be defined. Spies (1946b) has already noted a case that responded to liver extract after failing to respond to folic acid, and it is likely that others will be found; but it is clear, from the reports already published, that folic acid can produce remission in most cases.

In all of our cases gastric achlorhydria persisted throughout the present periods of observation.

SUMMARY

Synthetic folic acid has been given to 5 patients with true pernicious anæmia in relapse.

The folic acid produced clinical remissions, with return of the marrows to normoblastic from megaloblastic states, and a restoration of blood-counts towards normal levels. The achlorhydria gastrica persisted.

Folic acid was supplied through the courtesy of Lederle Laboratories Inc. to Boots Pure Drug Co. Ltd., who placed it at our disposal for this investigation.

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BENADRYL IN HAY-FEVER

A NOTE ON ITS ACTION

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'BENADRYL' (β -dimethylaminoethyl benzhydryl ether hydrochloride) is a new antihistamine compound synthesised by Rieveschl and Huber in the research laboratories of Parke, Davis and Co.

Studies on animals have shown that it has a powerful antihistamine and antispasmodic effect, as evidenced by the degree of protection it gives against histamine bronchospasm and anaphylactic shock (Loew et al. 1945, Wells et al. 1945). Clinical trials have shown that it is highly effective in the treatment of urticaria and angioneurotic cedema (Curtis and Owens 1945, O'Leary and Farber 1945, Todd 1946), in hay-fever (McElin and Horton 1945a and b, Koelsche et al. 1945), and, to a lesser degree, in asthma and various other allergic conditions. Its administration was shown to reduce the skin reactivity to histamine (McGavack et al. 1946). Its action is thought to be brought about by adsorption, at the site of action of histamine, by which it blocks the effect of the latter (Wells et al. 1945). Low toxicity, absence of the side-effects of parasympatholytic drugs, and relative freedom from untoward reactions, characterise this action (McGavack et al. 1946).

The present paper reports the effect of benadryl on the histamine and grass-pollen skin reactions of hay-fever patients.

METHODS

A group of five hay-fever patients (grass-pollen-sensitive) was investigated. They were all typical cases and had received no treatment previously. Each patient was given three doses of 100 mg. (two 50-mg. capsules) of benadryl by mouth during the first day of treatment, followed by three doses of 50 mg. a day for six days. No other treatment was given. Skin-tests were carried out with histamine (1% of the acid phosphate), grass-pollen extract (20,000 units per c.cm.), and control carbol-saline, (1) before treatment was started, (2) at the end of the first day of treatment, and (3) on comple-

tion of the treatment. The prick method of testing was used, and all tests were made on the flexor surface of the forearms. Details of the technique of the prick-test, recording the reactions, and their measurement by planimeter, have been described previously (Harley 1933, 1937).

RESULTS

Skin Reactions.—The results of the skin-tests are set out in composite form in the figure. They demonstrate an approximate fourfold reduction of the area of the skin reaction to grass-pollen extract and to histamine as the result of the first day's treatment (benadryl 300 mg.). This reduction was definite in each case, and the erythema was considerably less intense. After six days' treatment with benadryl 150 mg. a day the skin reactions had returned to about three-quarters of their original size.

Clinical Effects.—Of the five patients treated, three were promptly and completely relieved of their hay-fever and remained so until 12–24 hours after the treatment was stopped, when the symptoms recurred. One patient was greatly improved (estimated 75% relief), and one patient was not apparently benefited. Side-effects developing during the first day of treatment consisted of dryness of the mouth, slight drowsiness, and "muzziness" in the head. These symptoms abated when the dose of benadryl was reduced to 150 mg. a day.

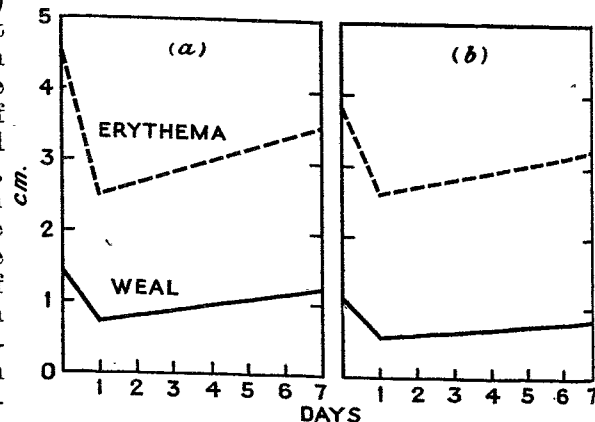
DISCUSSION

The histamine theory of the mechanism of the allergic diseases is based on the pioneer work of Dale and Laidlaw (1910) and Lewis (1926) and has received considerable support during recent years (Farmer 1941, Feldberg 1941). Briefly stated, it suggests that the allergic reaction is the expression of cellular damage produced by the special method of specific idiotoxin-idioreceptor union on or in the cells, and, in common with other forms of cellular damage, is attended by the liberation of histamine (or a histamine-like substance, "H-substance") from the cells participating in the reaction, and that it is this H-substance that produces the changes in the capillaries, smooth muscle, &c., which constitute the allergic reaction. Dale (1929)

believes that the reaction is due to the liberation of preformed histamine, present in the tissue cells, the union of idiotoxin with idioreceptor on or in the cells acting like other injurious stimuli.

The tests detailed above demonstrate that benadryl reduces equally the histamine skin sensitivity and the specific pollen skin sensitivity, and thus support the histamine theory of allergy.

With regard to the clinical value of the drug in the treatment of hay-fever, the few cases herein reported (owing to the very limited supply of benadryl available) are insufficient for an accurate assessment, but it seems likely that benadryl will abolish the need for pre-seasonal specific desensitisation in many patients. (It is estimated that the degree of reduction of the pollen skin sensitivity produced by the first day's treatment with 300 mg. of benadryl was equivalent to that produced by a course



Composite skin reactions of five hay-fever patients before, during, and after benadryl treatment showing average diameters of weal and erythema after prick-tests with (a) pollen and (b) histamine. Control-tests with carbol-saline gave negative results throughout.

of specific desensitisation with pollen extract to a dose of 20,000-30,000 units.) Possibly a combination of benadryl with co-seasonal specific treatment may become the method of choice, but that remains for further investigation to decide. As a palliative in urticaria too, the results in the few cases in which I have given it have been dramatically successful, and it seems not unlikely from the recent American reports that benadryl will be hailed as the greatest advance in the palliative treatment of the allergic diseases since the discovery of the action of adrenalaline.

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Preliminary Communication

FAT-DIGESTION IN SPRUE

STUDIED BY INTESTINAL INTUBATION

THE results of some preliminary investigations carried out to elucidate the mechanism of fat-digestion in subjects with tropical sprue are presented now, because few new cases are being encountered in the Royal Air Force, and other workers may be in a more favourable position to pursue the lines of investigation described.

Investigations have been carried out on ten patients invalided to this country with tropical sprue contracted in India, Burma, or Ceylon. Eight patients who had not served in tropical countries, had no present or past history of gastro-intestinal disorder, and were convalescent from orthopaedic operations, acted as controls.

On the morning of the examination patients received no breakfast. At 9 A.M. a radio-opaque double-lumen Miller-Abbott tube was passed into the small intestine by the technique used by Miller and Abbott.¹ The tube was swallowed to the 72-in. mark, when the tip was about 40 in. beyond the pylorus, radioscoping being used to ascertain that the tube was not coiled in the stomach. The balloon was then deflated. After an interval of 30 min., suction of about 100 mm. Hg was applied to the lumen of the tube in communication with the small intestine. A trap was arranged so that the material obtained was collected in a bottle surrounded with ice. After the fasting juice had been collected for about 20 min., the patient swallowed 25 ml. of olive oil. The suction was continued and, whenever any alteration was noted in the character of the aspirated material, the bottle was changed. Fat began to appear in 30-90 min. after it had been swallowed, and specimens were collected until they no longer contained fat.

RESULTS

To the naked eye the material aspirated from sprue patients differed strikingly from that of the normal controls (see figure). Whereas that of the controls had the appearance of a uniformly suspended bile-stained emulsion, that of the sprue patients consisted of whitish threads and clumps suspended in a relatively clear bile-stained fluid. Microscopically these threads and clumps contained numerous fat droplets enmeshed in mucin-like material. In material obtained from normal

patients droplets of similar size were seen, but they were evenly dispersed and not aggregated into clumps. In both the controls and the sprue patients most of the droplets stained blue with Nile blue sulphate (the specimens having been stored for 24 hours at 0° C), indicating the presence of fatty acids. Only a small proportion consisted of unsplit fat and stained pink, and this was well emulsified. Much of the mucoid material of the clumps also stained blue, suggesting the presence of fatty acids in a fine state of dispersal. Mucus stains (mucocarmine and thionin) showed small scattered conglomerations of mucus.

The extent of this abnormality varied in different patients. In some the clumps and threads were so abundant and thick that they blocked the tube, making aspiration very difficult, whereas in others they were much less plentiful. In general there was a rough correlation between the clinical severity of the disease and the degree of clumping.

In one patient the examination was carried out before and after successful treatment by diet and parenteral crude liver extract, and the character of the aspirated material changed considerably; clumps and threads in a fluid containing little emulsified fat gave place to only a few very small threads floating in a bile-stained emulsion of normal appearance.

It therefore appears that in the sprue syndrome fat is emulsified, and, as would be expected from stool fat-analysis, hydrolysed. The abnormality lies in either the aggregation into clumps and threads of the fatty material or the failure to disperse such aggregations if they occur as a transitory phase of normal digestion.

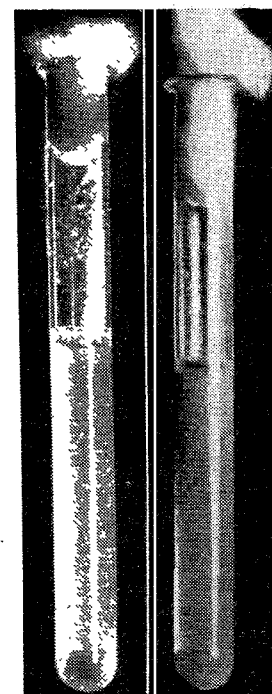
With the object of assessing the possibility of dispersing these clumps and threads, specimens of them from three patients were incubated at 37° C for 4 hours with fasting succus entericus:

- (1) From normal patients;
- (2) From normal patients with the addition of ox bile;
- (3) From a patient with mild sprue;
- (4) From a patient with mild sprue with the addition of ox bile;
- (5) From a patient with severe sprue;
- (6) From a patient with severe sprue with the addition of ox bile.

Good dispersal was obtained in (1), moderate dispersal in (3), and none in (5). The addition of ox bile to normal succus entericus (2) made no difference but did appear to increase the dispersal when added to sprue succus entericus (4) and (6). However, the dispersal was never so good as that obtained with normal juice.

DISCUSSION

The slender evidence we have obtained suggests that the clumps and threads consist mainly of fatty acids, both very finely dispersed and in droplet form, bound in a mucin-like matrix. Though it is generally agreed that mucus plays an important rôle in digestion, there is little detailed knowledge of its action. Mahlo and Mulli² have shown that it possesses both acid-combining and alkali-combining properties; and, despite little uniformity in experimental results, it seems fairly certain that mucin is considerably more resistant than other



(a) (b)
Succus entericus 90 min. after feeding 25 ml. of olive oil by mouth to (a) normal subject; (b) sprue patient.

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