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SULPHADIAZINE

Reports from the U.S.A. on the properties of sulphadiazine (2-sulphanilamidopyrimidine) continue to be favourable. It will be remembered that the chief advantages of this drug, apart from its wide applicability and a therapeutic effect at least equal to that of other sulphonamide compounds, are its freedom from toxic effects and the high concentration which can readily be maintained in the blood. Pharmacological studies such as those of G. J. Trevett, R. A. Nelson, and P. H. Long[1] explain these high blood concentrations as the effect of slow urinary excretion. Absorption is also slow, and with larger doses incomplete: a dose of 0.05 g. per kilogramme of body weight is well absorbed, but doubling this results in only a moderate increase in blood concentration. In this aspect of its behaviour the drug resembles sulphapyridine, and in very urgent cases an initial dose of sodium sulphadiazine given intravenously may be advisable. Comparatively little of the drug is acetylated, a fact which may have much to do with its therapeutic success, as the acetyl derivatives of sulphonamide compounds have no antibacterial action. There is fresh evidence of its therapeutic powers, both experimental and clinical. P. H. Long, E. A. Bliss, and E. Ott[2] have carried out therapeutic tests in mice, adding each of four sulphonamide compounds to their food in such amounts as to obtain so far as possible a uniform blood concentration of from 5 to 7 mg. per 100 c.cm. It is interesting that the drug concentration in the diet necessary to produce this was 1.0% for sulphathiazole, 0.8% for sulphanilamide, 0.5% for sulphapyridine, but no more than 0.1% for sulphadiazine. On this system of dosage sulphadiazine was as effective as sulphanilamide in treating haemolytic streptococcal infection and as sulphapyridine in treating pneumococcal infection, but inferior to sulphathiazole for the latter. This inequality of effect was obliterated by increasing the amount of sulphadiazine in the diet to 0.2%, thereby producing a blood concentration of 10 mg. per 100 c.cm.; increasing it to 0.5%, resulting in a blood level of 25 mg. per 100 c.cm., achieved an even higher recovery rate. There is no comparison with sulphathiazole in this experiment, but sulphapyridine given in the same dose is clearly outclassed. It also appears that sulphadiazine is at least as effective as sulphathiazole in treating staphylococcal infection in mice, though, as usual in this unsatisfactory form of experiment, it serves only to prolong survival into the second or third week.

On the clinical side, Trevett, Nelson, and Long[3] give the results of sulphadiazine treatment in forty-four cases of haemolytic streptococcal and twelve cases of staphylococcal infection, and in fewer cases of various other conditions; with these they were well satisfied. F. T. Billings and W. B. Wood[4] treated seventy-five cases of pneumococcal pneumonia with sulphadiazine alone, with only one death. In thirty more severe cases of pneumonia, sixteen having bacteriaemia, serum was given in addition: there were seven deaths, but the condition of six of the patients was hopelessly complicated by other disease. These authors, unlike Plummer and his colleagues, whose findings we quoted recently,[5] take the view that serum still has a place in the treatment of severe pneumonia, provided that dosage is large and controlled by the Francis skin test. H. F. Dowling *et al.*[6] also report the treatment of 115 cases of pneumococcal pneumonia, with thirteen deaths (11.3%): seventeen of these patients had bacteriaemia, and five of the deaths were in this group. This result differs in no significant way from those obtained by these and other authors from the use of sulphapyridine or sulphathiazole, and indeed it is doubtful whether any treatment will reduce the mortality of pneumonia much further, because there is always a proportion of cases in which some condition other than pneumonia itself gravely affects the prognosis. The main interest of all these papers lies not so much in the evidence they afford of therapeutic efficacy as in their uniform testimony to the freedom of sulphadiazine from most of the toxic effects which are now regarded as a necessary evil in sulphonamide treatment. Cyanosis is unknown; nausea and vomiting are rare, and are never severe. Only drug fever, skin rashes, and some mental disturbance seem to have been observed in more than very occasional cases, and such disturbances of haemopoiesis as have so far been noted were transient. The single fact that this drug rarely causes nausea is an inestimable blessing from the patient's point of view, and as soon as its properties become widely known it will be much in demand, if only for that reason.

But a word of warning must be uttered. Crystal formation and renal complications may result from sulphadiazine therapy, as with sulphapyridine.[7] Thomson, Herrell, and Brown at the Mayo Clinic[8] describe the case of a patient thirty-three years old who was given 75 to 90 grains of sulphadiazine daily for seven days. The urinary output steadily decreased from 600 c.cm. on the first day to *nil* on the eighth. The blood urea rose to 70 mg. per 100 c.cm. Cystoscopic examination under anaesthesia showed an empty bladder, and catheterization of the ureters gave a grating sensation in the lower part of each ureter due to crystallized sulphadiazine. The crystals were dislodged by moving the catheters gently to and fro, and the pelvis of both kidneys was freely irrigated with warm water. The first specimen of urine contained 390 mg. of sulphadiazine per 100 c.cm.—200 mg. as conjugated diazine and 190 mg. as free diazine. The urinary output immediately became normal, but twenty-four hours after catheterization the diazine content was 100 mg. per 100 c.cm.—48 mg. free and 52 mg. conjugated. The blood urea rose temporarily on the first day to 85 mg.,

[1] *Johns Hopk. Hosp. Bull.*, 1941, **69**, 303.
[2] Ibid., p. 297.
[3] Loc. cit.
[4] *Johns. Hopk. Hosp Bull.*, 1941, **69**, 314.
[5] *British Medical Journal*, 1941, **2**, 447.
[6] *J. Amer. med. Ass.*, 1941, **117**, 824.
[7] Leedham-Green, J. C., *British Medical Journal*, 1941, **1**, 586.
[8] *Proc. Mayo Clin.*, 1941, **16**, 609.

but fell to normal by the eighth day. The urine of this patient was alkaline in every determination except one during the course of administration of the drug. This is interesting in view of the report of Schwartz and his co-workers[9] concerning the importance of keeping the urine alkaline so as to diminish the formation of crystals in the urine of patients treated with this drug. The Mayo Clinic workers rightly insist that even alkalinization is secondary in importance to the main single factor —which is to maintain the urinary output at the figure of at least 1,500 c.cm. a day.

It is necessary to construct a table in which will be shown the solubility of all the sulphanilamide, pyridine, and sulphathiazole derivatives in water, saline, exuded serum, blood, and urine, both alkaline and acid. In the various accidents (with or without added infections) of aerial bombardment, this factor becomes an important one, for with a reduced volume of circulating fluid due to haemorrhage or shock, crystalluria may increase the burden already thrown on the kidneys.

VITAMIN B DEFICIENCY AND THE SMALL INTESTINE

It has been known for more than twenty years that deficiency of "vitamin B" is associated with abnormal gastro-intestinal function. When vitamin B_1 was recognized as a separate component of the B complex a great deal of attention began to be paid to the state of the gastro-intestinal tract in beriberi and in experimental polyneuritis. In the human disease constipation is common, and animal experiments have demonstrated reduced tone and motility in stomach and intestine.[10] It is these findings, incidentally, which are responsible for yet one more addition to the already overwhelming list of "cures" for constipation. More recently other members of the vitamin B complex have been implicated as essential for normal digestive activity. Much of this work is the result of careful radiological studies. It began with observations on the small intestine in cases of sprue (Pillai and Murthi,[11] Mackie[12]). In these and later studies, mainly by American workers, it was found that characteristic changes occurred in the small intestine in association with several diseases. Apart from tropical sprue, these were steatorrhoea, coeliac disease, ulcerative colitis, nephrosis, diabetes insipidus, and some cases of obstructive jaundice.[13] In early or mild disturbance of intestinal function motility and tonicity are increased, but later they are usually much diminished. Abnormal segmentation occurs, and there is often extensive alteration in the outline of the mucosal folds. As these radiological changes are most commonly found in the states of primary or secondary nutritive failure, they have come to be referred to as the "deficiency pattern" of the small intestine. The histological changes are on the whole rather vague. There is frequently atrophy of the muscular wall and of the mucosa; oedema, round-cell infiltration, and fibrosis may also be found. In one specimen, of which more will be said later, changes in the nervous elements were discovered.[14]

The cause of this functional disability of the intestine is obscure. There is growing evidence that one or more components of the vitamin B complex are associated with its development. The "deficiency pattern" has been produced in dogs on a diet lacking vitamin B, and was only completely cured by the administration of the whole complex.[15] The work of Martin and his colleagues[16] is of interest in this connexion. Dogs in which mild constipation had been induced were fed with barium sulphate, together with one or more of the various components of the vitamin B group, and frequent radiographs were taken. These workers examined the effect not only of the better-known components of the group—vitamin B_1, nicotinic acid, riboflavin, choline, pyridoxine (vitamin B_6), and pantothenic acid—but also of inositol, which has lately been shown to be an essential dietary factor for mice. Only inositol and nicotinic acid were found to have an effect. The former increased peristalsis in both stomach and small intestine; nicotinic acid, on the other hand, decreased peristalsis and induced a state of repose. The authors suggest that the balance of these two factors might determine the motility of the gastro-intestinal tract. That the vitamin B complex is probably responsible for the "deficiency pattern" in many of the patients showing intestinal abnormality is supported by therapeutic tests. Considerable recovery often follows the administration of liver extract.[17,18] As might be expected from the disturbed alimentary condition, oral administration may not be effective and the extract may have to be given parenterally. The deficiency of the vitamin B may be primary—that is, caused by a low dietary intake—or it may be secondary—that is, conditioned by a defective absorption of the vitamin because of some other pathological change in the intestine. In other words, the intestinal changes not only may result from the deficiency but might also be its cause. In either case the alimentary lesion will lead to still less adequate absorption of essential dietary factors, and a vicious circle is established. Lepore and Golden[19] find that the "deficiency pattern" in the small intestine is not confined to individuals with gross signs of diseases such as sprue. They describe a series of patients in whom the functional disorder of the intestine is accompanied by a series of symptoms and signs which, they claim, form a clear-cut syndrome due to deficiency of the vitamin B complex. There is usually a history of a diet rich in carbohydrate and poor in vitamin B. The patients complain of vague gastro-intestinal symptoms, anorexia, and asthenia. Objective findings include a flat glucose-tolerance curve, undoubtedly due to decrease in the absorptive powers of the intestine. The radiological findings were those of the "deficiency pattern." The oral administration of yeast extract was usually enough to produce rapid improvement: one patient who did

[9] Schwartz *et al.*, *J. Amer. med. Ass.*, 1941, **117**, 514.
[10] See, for example, Chatterjee, D. D., *Ind. J. med. Res.*, 1935, **23**, 191.
[11] *Ind. J. Med.*, 1931, **42**, 116.
[12] Mackie, T. T., *Med. Clin. N. Amer.*, 1933, **17**, 165.
[13] See Mackie, T.T., *J. Amer. med. Ass.*, 1941, **117**, 910; and Golden, R., ibid., 1941, **117**, 913.
[14] Golden, R., *Radiol.*, 1941, **36**, 262.
[15] Crandall, L. A., Chesley, F. F., Hansen, D., and Dunbar, J., *Proc. Soc. exp. Biol.*, N.Y., 1939, **41**, 472.
[16] *Amer. J. diges. Dis.*, 1941, **8**, 290.
[17] Mackie, T. T., and Pound, R. E., *J. Amer. med. Ass.*, 1935, **104**, 613.
[18] Mackie, T. T., Miller, D. K., and Rhoads, C. P., *Amer. J. trop. Med.*, 1935, **15**, 571.
[19] *J. Amer. med. Ass.*, 1941, **117**, 918.