titres against measles in patients with MS, as well as the delay in developing measles during childhood in these patients,²¹ seems to indicate a high resistance against that virus. Panelius *et al*²¹ showed not only that patients with MS contracted measles later than their siblings but also that men with MS tended to contract measles at an earlier age than women with the disease. The resistance of patients with MS to other types of micro-organisms has also been reported and supports the idea that such patients are higher responders to these micro-organisms.

If this hypothesis is true, serological studies might confirm the other observation of Panelius *et al* that histories of rheumatic fever were slightly less common in patients than in their siblings. This suggests that patients with MS have a higher resistance towards these micro-organisms. Nevertheless, nothing rules out the possibility that measles virus is directly related to the cause of the disease. The observation of Zabriskie *et al*²² that there is a decreased cell-mediated response to paramyxovirus in patients with MS conflicts with this view, and this finding should perhaps be regarded as being similar to the abnormal PPD reaction found in patients with MS a few years ago.³⁻⁵ These findings suggest that research, rather than focusing on a few exciting viruses or slow virus infections, should examine more closely the specific immune mechanism of patients with MS and its reaction to many types of infection.

The control of the immune response by genes related to the expression of the HLA antigens may be relevant. It has been well documented in animals that the genes controlling the expression of the transplantation antigens are closely linked to those controlling the expression of the immune response. Patients with MS have a higher incidence of HLA-3 and W 18 antigens than the normal population.¹⁷⁻¹⁹ The association of HLA-3 and W 18 in 30% of our patients compared with only 1.5% of 637 kidney recipients is another interesting observation, and we are currently investigating the relation between this association and the evolution of the disease. Patients with MS have a mixed lymphocyte culture determinant in common, identical with that associated with the HLA-7 and W 18 in normal people.²³ All these results reinforce the increasing evidence that the locus similar in the mouse to the well-known lactate dehydrogenase (LD) locus that controls the expression of the

immune response, abnormally controls this response in patients with MS.

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References

- Kabat, E A, Moore, D H, and Landow, H, *Journal of Clinical Investigation*, 1942, 21, 571.
- McAlpine, D, Lumsden, C E, and Acheson, E D, *Multiple Sclerosis*, 2nd edn. Edinburgh and London, Churchill Livingstone, 1972.
- Smith, H V, Hughes, I E, and Hunter, G, *Journal of Neurology, Neurosurgery and Psychiatry*, 1961, 24, 101.
- Marshall, J, and O'Grady, F, *Journal of Neurology, Neurosurgery and Psychiatry*, 1959, 22, 277.
- Miller, H, *et al*, *Journal of Neurology, Neurosurgery and Psychiatry*, 1961, 24, 118.
- Lamoureux, G, and Borduas, A G, *Clinical and Experimental Immunology*, 1966, 1, 363.
- Adams, J M, and Imagawa, D T, *Proceedings of the Society for Experimental Biology and Medicine*, 1962, 111, 562.
- Lamoureux, G, *et al*. In preparation.
- Lamoureux, G, *et al*, *Neurology*, 1975, 25, 537.
- World Health Organisation, Respiratory Virus Disease, Technical Report Series No 170, p 48. Geneva, WHO, 1959.
- Lamoureux, G, *et al*, *Annals de l'Institut Pasteur*, 1970, 118, 562.
- Jondal, M, Holm, G, and Wigzell, H, *Journal of Experimental Medicine*, 1972, 136, 207.
- Wybran, J, and Fudenberg, H, *Journal of Clinical Investigation*, 1973, 52, 1026.
- Lamoureux, G, *et al*, *Union Medicale du Canada*, 1972, 101, 674.
- Lamoureux, G, *et al*, *La Vie Médicale au Canada Français*, 1974, 3, 479.
- Jersild, C, Svejgaard, A, and Fog, T, *Lancet*, 1972, 1, 1240.
- Jersild, C, *et al*, *Tissue Antigens*, 1973, 3, 243.
- Naito, S, *et al*, *Tissue Antigens*, 1972, 2, 1.
- Bertrams, J, Kuwert, E, and Liedtke, U, *Tissue Antigens*, 1972, 2, 405.
- Currier, R D, *et al*, *Neurology*, 1974, 24, 748.
- Panelius, M, *et al*, *Acta Neurologica Scandinavica*, 1973, 42, 89.
- Utermohlen, V, and Zabriskie, J B, *Journal of Experimental Medicine*, 1973, 138, 1591.
- Jersild, C, *et al*, *Transplantation Proceedings*, 1973, 5, 1791.

Intestinal absorption in normal Indian and English people

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Summary

The absorption of glycine, glycyglycine, water, and electrolytes was studied by intestinal perfusion in normal Indian and English people. Compared with the English people the Indians showed impaired absorption of all four substances. In the Indians the absorption of glycine and glycyglycine was impaired to the same extent, so

that the kinetic advantage of glycyglycine as compared with glycine was preserved. The reduced absorption in the Indians may be the functional counterpart of the minor morphological changes seen in the jejunal mucosa of people living in southern India.

Introduction

Normal Indian and English people differ in the structural appearance of their small intestinal mucosa.^{1,2} Evidence of a functional difference, however, rests principally on studies of xylose and fat excretion,^{3,4} which are at best indirect methods of quantifying absorption. We have therefore used the more direct method of intestinal perfusion to quantify and compare amino-acid and dipeptide absorption in apparently normal Indian and English people.

Subjects and methods

The English people (six men) had been studied previously in London by MDH.⁵ The Indians (10 men) were admitted to this unit

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for metabolic studies. All were either normal volunteers or patients admitted with minor gastrointestinal symptoms, and in none was there any suspicion or evidence of small-bowel disease. In all cases the nature of the investigation was explained and the subject's consent obtained. The age distribution was comparable in the two groups. Absorption studies with fat, xylose, and vitamin B₁₂ and jejunal biopsy were carried out as described.⁶

Perfusion of the proximal 30 cm of jejunum was carried out with a double-lumen tube incorporating a proximal occlusive balloon.⁵ The perfusion solutions were glycine 20 mmol/l and glycylglycine 10 mmol/l containing polyethylene glycol 4 g/l made isotonic with saline and with the pH adjusted to 7.0. Solutions were perfused at a constant 15 ml/min. For each solution, after a 30-minute equilibration period three 10-minute collections were made from the distal end of the test segment. All samples were collected on ice. Samples for dipeptide analysis were immediately acidified to pH 1.0. All samples were centrifuged to removed particulate matter and stored at -20°C to await analysis.

Amino-acids and dipeptides were measured by paper chromatography,⁷ polyethylene glycol was measured by the method of Hyden,⁸ and electrolytes were determined by standard methods. When glycylglycine absorption was being studied free glycine accumulated in the perfusate. This free glycine was assumed to have been liberated by hydrolysis at the brush border and was therefore subtracted from the amount of glycylglycine that had disappeared from the perfusate to determine the amount absorbed. Absorption rates were calculated using standard formulae.⁵

Results

In the English people the absorption of fat and xylose was normal. None of the Indians had steatorrhoea or vitamin B₁₂ malabsorption, but three had a reduced five-hour urinary xylose excretion (13%, 17%, and 22%). The jejunal biopsy specimens from the Indians were similar to those from apparently healthy Indians described previously.²

Amino-acid and dipeptide absorption—Significantly less glycine ($P < 0.0005$) and glycylglycine ($P < 0.0025$) was absorbed by the Indians than by the English people (fig 1), the mean values being 31% less in each instance. This suggested that the uptake mechanisms for both the free amino-acid and the dipeptide were equally affected.

FIG 1—Absorption of 20 mmol glycine and 10 mmol glycylglycine in normal English (○) and Indian (●) people. Absorption expressed as mmol glycine absorbed per hour over 30 cm jejunum. Horizontal lines represent means.

In both groups the absorption of glycine when presented as the dipeptide was significantly greater than when presented as the free amino-acid ($P < 0.01$ in both groups). This kinetic advantage, as measured by the percentage increase in mean glycine absorption, was the same in the Indian group (30%) as in the English group (29%) despite the overall reduction in absorptive capacity in the Indians.

Sodium and water absorption—Sodium and water absorption in the presence of both glycine and glycylglycine was reduced in the Indians, the reduction being statistically significant in all cases except for the absorption of sodium from glycine solutions (fig 2). Chloride move-

FIG 2—Absorption of water (□) and sodium (▨) from solutions of glycine and glycylglycine in normal Indian and English people. Columns represent means, and vertical lines and bars represent standard deviations. NS = Not significant.

ment in all cases paralleled sodium movement and is not considered separately. To some extent the reduction of sodium and water absorption may be explained on the basis of the reduction in amino-acid and dipeptide uptake in the Indians; however, the sodium and water absorbed per mole of non-electrolyte by the Indians was still less than that in the English group. As these observations were based on net fluxes it is not possible to say whether the changes were due to an alteration of the sodium/amino-acid interaction at the uptake stage or to increased sodium efflux into the lumen.

No correlations were found between the results of the perfusion studies and the tests of absorption or the jejunal histology.

Discussion

The Indians in this study were similar in all respects to normal southern Indians investigated previously.⁴ Earlier studies had suggested that normal Indian people do not absorb xylose and fat as well as normal Western people do.^{3,4} This study, employing a direct measure of absorption, with identical techniques in both groups, unequivocally establishes the lower absorptive capacity of the upper jejunum of Indians for amino-acids, dipeptides, water, and electrolytes as compared with normal English people. This reduced absorption may be genetically determined, as is the case with lactose absorption and the reduced lactase levels found in normal Indians.⁹ It is more likely, however, that it is acquired and is a result of the process responsible for the mild histological abnormalities seen in these patients and which are widely prevalent in the tropics.

Theoretically several factors may be responsible for these functional and structural changes.² Parasitic infestation may cause intestinal damage, but no parasites were found in any person in this study. Intraluminal bacteria may produce absorptive defects, as in the stagnant-loop syndrome. Bacteria are more numerous in the upper small intestine of Indian people than in people in the West, but histological changes do not parallel bacterial counts.¹⁰ Moreover, bacteria are much more numerous in the lower small bowel, where histological changes are less pronounced. Of course, qualitative studies might indicate the presence of particular organisms within the jejunum capable of producing specific mucosal toxins, but none have been identified. Viral isolates were obtained from 58% of faecal specimens collected at random from southern Indian children,¹¹ and some 90% of apparently healthy southern Indian adults excrete virus-like particles in their stools, suggesting a continued viral infection of the gastrointestinal tract.¹² Such a continuing infection may result in functional damage.

Finally, nutritional deficiencies may affect intestinal structure and function. Protein deficiency has been suspected as a cause of structural change but available data are inconclusive and uncontrolled. Patients in temperate regions with hypoproteinaemia due to dietary or renal causes have normal intestinal histology.^{13,14} Iron, vitamin B₁₂, and folate deficiencies have all

been incriminated as responsible for small-intestinal mucosal change, but these deficiencies were absent or only marginal in the present series.

If the reduced absorptive capacity of the upper jejunum in Indians is representative of the function of the whole small intestine, this finding may be of considerable nutritional importance, particularly for populations with an inadequate or only marginally adequate diet. Furthermore, if the observed defect of absorption is acquired, elucidation of the causative factors and their elimination could make a substantial contribution to improving the nutritional status of the community.

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References

- ¹ Baker, S J, *et al*, in *Intestinal Biopsy, Ciba Foundation Study Group*, No 14, ed G E W Wolstenholme and M P Cameron, p 84. London, Churchill, 1962.
- ² Baker, S J, *Pathologia et Microbiologia*, 1973, 39, 222.
- ³ Baker, S J, Jacob, R, and Mathan, V I, *Indian Journal of Medical Research*, 1971, 59, 1869.
- ⁴ Baker, S J, and Mathan, V I, *American Journal of Clinical Nutrition*, 1972, 25, 1047.
- ⁵ Hellier, M D, *et al*, *Gut*, 1972, 13, 965.
- ⁶ Mathan, V I, Swarnabai, S, and Baker, S J, *Indian Journal of Medical Research*, 1973, 61, 714.
- ⁷ Das, M, and Radhakrishnan, A N, *Biochemical Journal*, 1973, 135, 609.
- ⁸ Hyden, S, *Kungliga Lantbrukshögskolans Annaler*, 1955, 22, 139.
- ⁹ Swaminathan, N, *et al*, *Clinica Chimica Acta*, 1970, 30, 707.
- ¹⁰ Bhat, P, *et al*, *Gastroenterology*, 1972, 62, 11.
- ¹¹ John, T J, personal communication, 1972.
- ¹² Mathan, M, *et al*, *Lancet*, 1975, 1, 1068.
- ¹³ Gough, K R, *et al*, *Quarterly Journal of Medicine*, 1963, 32, 243.
- ¹⁴ Jansen, H, Jarnum, S, and Hansen, J P H, *Nephron*, 1966, 3, 209.

Bleomycin in advanced squamous cell carcinoma: a random controlled trial

Report of Medical Research Council Working Party on Bleomycin*

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Summary

Bleomycin was compared with conventional cytotoxic drugs in the treatment of 70 patients with advanced squamous cell carcinoma; the primary deposit was in the head and neck in 50 patients and in the perineum or skin in 20. Thirty-four patients received bleomycin while 36 received other cytotoxic drugs. No significant difference was detected between the two groups either in the proportion showing tumour regression or in the survival rates. If bleomycin is to advance the treatment of squamous cell carcinoma it can be only in combination with other drugs or with radiotherapy.

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Introduction

An uncontrolled trial has confirmed that bleomycin has significant clinical activity, but the response of patients with various types of tumours to bleomycin alone was poor.¹ We therefore conducted a randomised controlled trial comparing bleomycin with other cytotoxic drugs to determine the drug's effectiveness in treating patients with squamous cell carcinoma.

Patients and methods

Patients with well-differentiated squamous cell carcinoma in the mouth, pharynx, larynx, oesophagus, perineum, or skin were eligible for entry to the trial. The tumour had either to be too far advanced for an attempt at curative surgery or radiotherapy or, as was more common, to have recurred after surgery or radiotherapy. Only those patients who had a reasonable expectation of life and were easily accessible for treatment and follow-up were selected.

On entry to the trial, after inquiry by telephone to the MRC Statistical Research and Services Unit, the patient was given bleomycin treatment or treatment with other drugs. Patients were randomly allocated to the two treatment groups after stratification according to the treatment centre, the sex, and the following subsites within the sites mentioned above: buccal mucosa, gums, hard palate, floor of mouth, tongue, oropharynx, nasopharynx, pyriform sinus, post-cricoid, posterior pharyngeal wall, supraglottic, glottic, or subglottic regions, cervical oesophagus, intrathoracic oesophagus, vulva, penis, scrotum, and anal orifice.

In the bleomycin group our intention was to give bleomycin 30 mg intramuscularly twice a week to a total of 300 mg if this was tolerated. We allowed a reduction in dose for extreme age in a few patients, and the dose was modified for other reasons too (see table II). Most patients were treated as outpatients. In the other group the clinician in charge used the cytotoxic drug and regimen of his choice. In both groups further chemotherapy or radiotherapy could be given after failure of treatment. Patients in both groups received analgesics, blood transfusions, surgical procedures to relieve pain, or steroids as considered necessary. Routine chest radiographs and haematological and biochemical investigations were carried out on all patients before, during, and after treatment.

Results

Seventy patients entered the trial; their distribution between treatments according to tumour site, sex, and age is shown in table I.