

the number of tumour cells is small¹³ we are conducting a trial using local treatment plus adjuvant chemotherapy versus local treatment alone in patients at high risk for relapse to see if the addition of drugs early in treatment improves the prognosis in this group. Randomized studies are also under way to see if the number of drugs in the combination can be reduced without loss of therapeutic effect, and we are investigating the use of chemotherapy instead of radiotherapy preoperatively. If effective, the normal tissue would be undamaged at operation, which would be an advantage for the surgeon. Radiotherapy could be given later.

Our results also show that it is preferable to give antitumour drugs over short periods—for example, about 36 hours. The theoretical basis for this approach has been known for some time,¹⁴ the clinical application has been outlined,^{15 16} and it has been shown to work in practice.^{5 17} This approach has the advantages of a considerable reduction in bone marrow toxicity, a shorter stay in hospital for the patient, and a drastic reduction in the need for intensive supportive systems such as platelet transfusions and antisepticaemia regimens. The traditional practice of automatically administering antitumour drugs over five days or longer should be reconsidered. These initial results lead us to agree with Bertino *et al.*'s prediction that the increasing application of newer concepts of tumour cell kinetics and the addition of drug therapy to surgery and radiotherapy may lead

to an improved outlook for these patients in the next few years.¹⁸

Requests for reprints should be addressed to L.A.P.

References

- 1 James, A. G., *Cancer Prognosis Manual*. New York, American Cancer Society, 1966.
- 2 Carter, S. K., and Soper, W. T., *Cancer Treatment Reviews*, 1974, 1, 5.
- 3 Livingston, R. B., and Carter, S. K., *Single Agents in Cancer Chemotherapy*. New York, I.F.I./Plenum, 1970.
- 4 Broder, L. E., and Tormey, D. C., *Cancer Treatment Reviews*, 1974, 1, 183.
- 5 Price, L. A., and Goldie, J. H., *British Medical Journal*, 1971, 4, 336.
- 6 Hill, Bridget, T., and Baserga, R., *Cancer Treatment Reviews*, in press.
- 7 Hill, Bridget, T., personal communication.
- 8 Mosher, M. B., De Conti, R. C., and Bertino, J. R., *Cancer*, 1972, 30, 56.
- 9 Nervi, C., Casale, C., and Cortese, M., *Tumori*, 1969, 55, 103.
- 10 Cortes, E. P., *et al.*, *Proceedings of the American Association for Cancer Research*, 1972, 13, 86.
- 11 Hanham, I. W. F., Newton, K. A., and Westbury, G., *British Journal of Cancer*, 1971, 25, 462.
- 12 Jacquillat, C., *et al.*, *Presse Médicale*, 1967, 75, 1321.
- 13 Wilcox, W. S., *et al.*, *Cancer Chemotherapy Reports*, 1965, 47, 27.
- 14 Bruce, W. R., Meeker, B. E., and Valeriote, F. A., *Journal of the National Cancer Institute*, 1966, 37, 233.
- 15 Bergsagel, D. E., *Modern Medicine of Canada*, 1969, 24, 19.
- 16 Price, L. A., *Proceedings of the 3rd Vinca Alkaloids Symposium*, ed. W. H. Shedden. Basingstoke, Eli Lilly and Co, 1973.
- 17 Goldie, J. H., and Price, L. A., in press.
- 18 Bertino, J. R., Mosher, M. B., and De Conti, R. C., *Cancer*, 1973, 31, 114.

Diarrhoea in Thyroid Medullary Carcinoma: Role of Prostaglandins and Therapeutic Effect of Nutmeg

J. A. BARROWMAN, A. BENNETT, P. HILLENBRAND, K. ROLLES, D. J. POLLOCK, J. T. WRIGHT

British Medical Journal, 1975, 3, 11-12

Summary

In a patient with medullary carcinoma of the thyroid with pulmonary metastases who presented with diarrhoea and steatorrhoea large amounts of prostaglandin-like material were present in peripheral blood, and some was extracted from the tumour. The diarrhoea which persisted after thyroidectomy responded to treatment with nutmeg.

Introduction

Medullary carcinoma of the thyroid is a rare member of the group of endocrine tumours which may secrete polypeptide or amine hormones. The tumour, which arises in the thyroid C cells,¹ contains and secretes large amounts of calcitonin.² Large quantities of material similar to prostaglandins E₂ and F_{2α} have

also been found in these tumours and in the venous blood draining them.³ 5-Hydroxytryptamine has been isolated from the C cells,⁴ and increased blood and urinary levels of 5-hydroxyindole acetic acid found in patients with medullary carcinoma of the thyroid.⁵

Diarrhoea occurs in about 30% of patients with this disease and may be associated with large fluid, electrolyte, and weight loss and steatorrhoea; a combination of hormonal factors may be responsible.^{4 6} Calcitonin does not seem to affect gut motility,⁷ but prostaglandins can cause diarrhoea,⁸ and other agents present in these medullary tumours including 5-hydroxytryptamine,⁵ histaminase, and kallikrein⁹ may be partly responsible for diarrhoea.

Case Report

A 41-year-old woman complained of watery diarrhoea and a weight loss of 13 kg over two years. She noticed frequent borborygmi and passed about five foul-smelling stools each day with urgency and occasionally incontinence. Her diarrhoea had been partially controlled with codeine and diphenoxylate with atropine (Lomotil). There was evidence of recent weight loss, and a hard irregular fixed mass was found in the left lobe of the thyroid. Several hard matted lymph nodes occurred in the left jugular chain and one in the left supraclavicular fossa. Frequent loud abdominal borborygmi were heard.

Investigations showed mild steatorrhoea (8 g fat daily) and a serum carotene level of 0.242 μmol/l (13 μg/100 ml). A thyroid scan showed no uptake of ¹²⁵I over the left lobe. The gastrointestinal tract appeared structurally normal on barium meal and follow-through examination, but the transit time was rapid: barium reached the rectum in just over one hour. Chest x-ray examination showed miliary mottling of both lungs, suggesting the presence of disseminated carcinoma. The total prostaglandin-

Department of Gastroenterology, The London Hospital, London E1 1BB

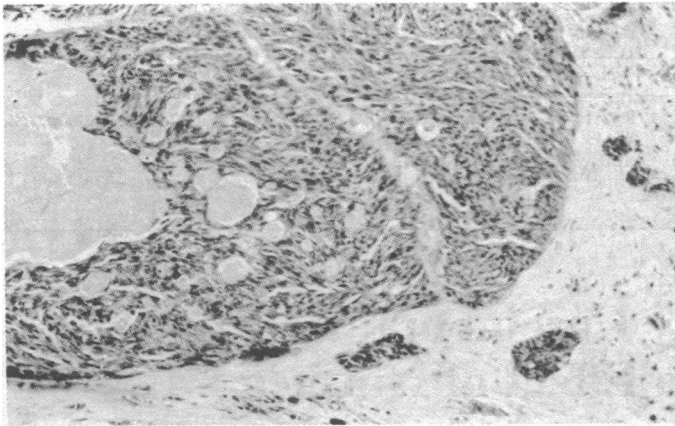
J. A. BARROWMAN, PH.D., M.R.C.P., Senior Lecturer
P. HILLENBRAND, M.B., M.R.C.P., Senior Registrar
K. ROLLES, B.SC., M.B., House Physician
J. T. WRIGHT, D.M., F.R.C.P., Consultant Physician

Department of Pathology, The London Hospital, London E1 1BB
D. J. POLLOCK, M.B., M.R.C.PATH., Senior Lecturer in Pathology

Department of Surgery, King's College Hospital Medical School, London SE5 8RX
A. BENNETT, PH.D., Reader in Pharmacology

like material extracted from peripheral venous plasma and assayed biologically¹⁰ was equivalent in activity to 5.4 pg/l prostaglandin E₂. This is about five times greater than normal.

Medullary carcinoma of the thyroid was diagnosed and a total thyroidectomy with lymph node dissection of the neck performed. Histological examination showed extensive invasion of the thyroid by a medullary carcinoma of spindle-cell type in which there was much cellular pleomorphism and many mitoses; some amyloid was present (see photograph). Associated lymph nodes had been replaced with tumour. Tumour extracts after homogenization in acid ethanol showed prostaglandin-like activity of 7 ng/g prostaglandin E₂. Extracts of homogenates in Krebs solution showed activity equivalent to 30 ng/g indicating that the tissue could synthesize prostaglandins.¹¹ After surgery urinary excretion of 5-hydroxyindole acetic acid and 4-hydroxy-3-methoxy mandelic acid was normal.



Medullary carcinoma of the thyroid showing predominantly spindle cell pattern and deposition of amyloid (left). (Haematoxylin and Eosin $\times 78$.)

The diarrhoea did not regress after operation and the patient became anorexic, though the plasma level of prostaglandin-like material was normal (0.5 pg prostaglandin E₂ equivalents/l). An average of 6.7 stools were passed daily despite treatment with codeine and Lomotil. These drugs were replaced by ground nutmeg¹² one teaspoonful nine times a day by mouth. At this dose none of the toxic effects of nutmeg, which resemble those of atropine, were seen. Nutmeg is a potent inhibitor of prostaglandin synthesis. The stool frequency was reduced within two to three days to a daily average of 2.6 and stools became more solid but their weight remained at 315 g, possibly because the patient's appetite improved.

After about a month a hydrophilic colloid (psyllium) 5 ml twice a day was also given, and indomethacin (another inhibitor of prostaglandin synthesis) 25 mg three times a day was prescribed as stool frequency had increased slightly. Six months later stools occurred once or occasionally twice daily and the patient felt well. Chest x-ray pictures taken three months after operation showed no change in the miliary mottling, though subsequent pictures have shown increased mottling.

Discussion

Prostaglandins seemed to contribute to this patient's diarrhoea, for circulating levels of prostaglandin-like material were high. Normally prostaglandins are cleared from the blood by several tissues including the lungs, but the multiple pulmonary metastases may have released prostaglandins or interfered with their local inactivation. Circulating prostaglandins may have increased motility and "hurry" by an effect on the gut muscle or, more likely, by increasing the amount of fluid in the gut.⁸ Prostaglandin E₂ administered into the gut causes diarrhoea characterized by formed faeces in clear fluid^{13 14} and a secretion of fluid into the lumen.¹⁵ Similarly, intravenous infusion of prostaglandin F_{2 α} increases water and electrolyte secretion by the small intestine though not by the colon.¹⁶ The intestinal hurry in our patient might have caused the mild steatorrhoea.

The possible contribution of prostaglandins to the diarrhoea was also supported by the patient's response to nutmeg, since nutmeg is a potent inhibitor of prostaglandin synthesis in human isolated colonic mucosa and a non-selective depressant of the responses of rat stomach muscle to prostaglandins.¹⁷ The response to indomethacin was consistent with this theory. Nevertheless, other substances may also mediate the diarrhoea, and nutmeg (*Myristica fragrans*), which is a mixture of volatile oils, fats, myristicin, elemicin, and saffrole, may act in a variety of ways. As nutmeg's toxic effects resemble those of atropine an anticholinergic effect might have contributed to the anti-diarrhoeal activity, but Schlemmer *et al.*¹⁸ consider that sympathomimetic effects, particularly those of elemicin, may be responsible.

A controlled trial of nutmeg was not possible in our patient, but the clinical response was striking and confirmed the findings of others.¹² Our results also support the possibility that prostaglandins are responsible, at least in part, for the diarrhoea associated with medullary carcinoma of the thyroid when lung metastases are present and that nutmeg may act by interfering with the synthesis or actions of prostaglandins.

References

- Pearse, A. G. E., *Proceedings of the Royal Society, Series B*, 1966, 164, 478.
- Sieber, P., *et al.*, *Helvetica Chimica Acta*, 1968, 51, 2057.
- Williams, E. D., Karim, S. M. M., and Sandler, M., *Lancet*, 1968, 1, 22.
- Falck, B., *et al.*, *Acta Physiologica Scandinavica*, 1964, 62, 491.
- Williams, E. D., Brown, C. L., and Donaich, I., *Journal of Clinical Pathology*, 1966, 19, 103.
- O'Higgins, N. J., *British Journal of Hospital Medicine*, 1973, 9, 509.
- Bernier, J. J., *et al.*, *Gut*, 1969, 10, 980.
- Bennett, A., and Flesher, B., *Gastroenterology*, 1970, 59, 790.
- Baylin, S. B., *et al.*, *New England Journal of Medicine*, 1970, 283, 1239.
- Unger, W. G., Stamford, I. F., and Bennett, A., *Nature*, 1971, 233, 336.
- Bennett, A., Stamford, I. F., and Unger, W. G., *Journal of Physiology*, 1973, 229, 349.
- Fawell, W. N., and Thompson, G., *New England Journal of Medicine*, 1973, 289, 108.
- Horton, E. W., *et al.*, *Gut*, 1968, 9, 655.
- Misiewicz, J. J., *et al.*, *Lancet*, 1969, 1, 648.
- Matuchansky, C., and Bernier, J. J., *Gut*, 1971, 12, 854.
- Cummings, J. H., *et al.*, *Clinical Science and Molecular Medicine*, 1974, 46, 15P.
- Bennett, A., Gradidge, C. F., and Stamford, I. F., *New England Journal of Medicine*, 1974, 290, 110.
- Schlemmer, R. F., *et al.*, *New England Journal of Medicine*, 1973, 289, 922.