Diarrhoea associated with medullary carcinoma of the thyroid¹

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SUMMARY Diarrhoea, which is present in roughly one third of cases of medullary carcinoma of the thyroid, was investigated in five cases.

Excessive loss of water and electrolytes in the stools was the major factor. Steatorrhoea was mild or absent, and intestinal absorption of glucose and vitamin B₁₂ was normal; the histological appearance of the small intestinal mucosa was normal or subnormal. Water and sodium diarrhoea seems to be linked to a sometimes considerable increase in the rate of transit through the small intestine and colon, and may be relieved by codeine or codethyline. The frequent increase in the maximum blood sugar level during an oral tolerance test should not be interpreted as evidence of a para-diabetic condition. In fact, the intravenous glucose tolerance test is usually normal and the excessive rise in blood sugar after oral administration seems to be the consequence of the increased rate of transit through the small intestine.

The link between the tumour and the disordered motility seems definite in view of certain cases in which removal of the tumour caused the diarrhoea to disappear immediately. Production by the tumour of serotonin or other derivatives of tryptophan or of kallikrein, which activates bradykinin, is rare. With regard to prostaglandins, high concentrations have been observed in the tumours and in the venous blood draining the tumours, but their presence in systemic blood is inconstant. The only hormonal substance, concentration of which seems to be definitely increased in the systemic blood of patients with a medullary carcinoma of the thyroid, is thyrocalcitonin but this hormone does not seem to have any effect on the motor activity of the digestive tract.

Since the first descriptions by Williams (1966) and Bernier, Bouvry, Cattan, and Prost (1966) diarrhoea associated with medullary carcinoma of the thyroid has been reported on several occasions (Bernier, Savoie, Garnier, Cattan, Bouvry, Rambaud, Bognel, and Prost, 1967; Hillemand, Gilbert-Dreyfus, Debray, and Cattan, 1967; Ibanez, Cole, Russel, and Clark, 1967; Davis, 1967; Cope and Williams, 1967). In these publications the authors attempted mainly to determine the frequency and pathogenesis of this association. However, there has not yet been published a full analysis of the clinical, biological, radiological, and histological characteristics of the disturbance in intestinal function. We have attempted to present in this paper such a study based on five personal cases.

CASE REPORTS

CASE 1 This case has already been reported in detail by Bernier *et al* (1966).

¹This paper was presented at the scientific meeting of the British Society of Gastroenterology held in London November 1968.

Mr D., aged 50 years, a metal analyst, was admitted to hospital on 21 April 1964 for chronic diarrhoea which came on suddenly in March 1963. He had lost 10 kg in weight. On examination an inactive nodule of the right lobe of the thyroid was found, with enlarged right cervical lymph nodes. A total thyroidectomy and block dissection of the right cervical lymph nodes was carried out in July 1964. The histology showed a medullary carcinoma of the thyroid with deposits of amyloid. Immediately after the operation diarrhoea disappeared. The patient is still apparently cured four years later. Small doses of thyroxine have been given since the operation.

CASE 2 This case also has been reported in detail by Bernier *et al* (1967).

Miss Z., aged 17 years, was admitted to hospital on 10 July 1966 for chronic diarrhoea. She was underweight (15 kg). In 1960 a non-toxic nodule of the left lobe of the thyroid was discovered, with bilateral cervical lymphadenopathy which had probably been present since 1956. A total thyroidectomy with block dissection of the right cervical lymph nodes was carried out in July 1960, and the left cervical lymph nodes were removed in October

1960. The patient has since been receiving maintenance doses of thyroxine. In 1965 enlarged lymph nodes were discovered close to the right trapezius muscle together with pulmonary metastases. The diarrhoea, which had been present since 1956, disappeared for 15 days after the operation in July 1960, but recurred afterwards. Since 1962 the patient has complained of postprandial flushing, localized to the face. Growth was considerably retarded and puberty had not yet begun. The right trapezial lymph nodes were removed in October 1966. Histology showed lymph node metastases from a medullary carcinoma of the thyroid with amyloid stroma. The diarrhoea continued unchanged but disappeared on daily oral administration of 60 mg of codeine.

CASE 3 Mr B, aged 54 years, a company director, was admitted on 10 June 1967 for chronic diarrhoea. He had lost 15 kg in weight. In 1950 a left subtotal thyroid lobectomy was carried out with block dissection of the left cervical lymph nodes for a tumour of the left lobe of the thyroid. Left cervical lymph node enlargement had been noted in 1947, and left cervical radiotherapy had been carried out in 1957 for residual lymph node enlargement. In 1963 right cervical lymph nodes appeared. A block dissection of the right cervical lymph nodes was carried out in January 1967, followed by cobalt radiotherapy to the neck. Histology showed metastases from a medullary carcinoma of the thyroid with amyloid stroma. The diarrhoea came on gradually in 1963. On examination there were small enlarged lymph nodes in the deep cervical and occipital areas. Liver metastases were discovered on peritoneoscopy and endoscopic biopsy. Maintenance doses of thyroxine have been given since January 1968. Diarrhoea disappeared for 10 months on daily oral administration of 60 mg of codeine and 60 mg of codethyline. Diarrhoea recurred in August 1968, at which time hepatomegaly was striking.

CASE 4 This case was reported in detail by Hillemand *et al* (1967).

Mr C., aged 56 years, a draughtsman, and patient of Dr Hillemand, was admitted to Professor Debray's unit in July 1965 for chronic diarrhoea which had been present since September 1964. He had lost 25 kg in weight. A nodule in the right lobe of the thyroid gland had been present since 1946. In July 1965 the patient complained of pain in the bones, and multiple bony lacunae were discovered in the ribs, the pelvis, and the vertebral column. A ^{131}I uptake test was carried out and proved negative both in the case of the thyroid nodule and the metastases. Total thyroidectomy was carried out in August 1965 and histology showed medullary carcinoma of the thyroid with amyloid stroma. Diarrhoea persisted, and the patient died from cachexia on 27 December 1965. There was no postmortem examination.

CASE 5 Mr C., aged 41 years, formerly a butcher, was admitted to hospital on 28 January 1968 referred by Professor Tubiana for chronic diarrhoea (weight loss 5.5 kg). In 1938 a calcified nodule in the right lobe of the thyroid was found. In 1957 dysphagia appeared and in 1958 huge bilateral cervical lymph nodes. In 1959 a

lymph node biopsy was carried out, followed by cobalt radiotherapy. A further biopsy was carried out in 1967. Histology showed metastases from a medullary carcinoma of the thyroid with amyloid stroma. Since then large tumours of the thyroid and cervical lymph nodes have persisted, compressing the upper digestive tract and replacing the normal thyroid tissue. Thyroid extract has been given since 1960. Diarrhoea, which started in 1961, has increased in intensity since 1965. It disappeared from February 1968 onwards after the administration of codeine, 45 mg daily.

Three negative points are common to these five cases: (1) nothing was obtained from the patients' past or family histories; (2) none of the patients had had a phaeochromocytoma detectable by clinical or the usual laboratory investigations; (3) all the patients were euthyroid (in some cases due to substitution therapy) during investigation of the diarrhoea.

METHODS

The patients were investigated in a clinical unit on a controlled diet, the fat content of which was about 70 g per 24 hours. The number and weight of the stools were measured daily.

A complete stool analysis was carried out (Goiffon and Goiffon, 1961), the following measurements being carried out on 24-hour samples: faecal fat by extraction by Kumagawa's method; chloride, sodium, and potassium by Goiffon's technique (Goiffon, Goiffon, and Fron, 1961a and b). The results are the mean of three estimations carried out on three successive days.

The transit time was determined by ingestion of a tablet containing carmine red, and noting the time at which the stools became coloured. The transit time through the small intestine and colon was determined by x-ray films taken every half hour when the patient was fasting, after swallowing two dessert spoonfuls of barium.

A glucose tolerance test was carried out by measuring the blood glucose level (Hoffman, 1931) after the ingestion of 50 g of glucose in 250 ml of water. The coefficient of glucose assimilation was determined by measuring the rate of decrease in blood glucose after rapid intravenous injection of 0.3 g/kg body weight of glucose in a 30% solution. Urinary excretion of D-xylose was measured during the five hours after ingestion of 25 g of this pentose. The absorption of ^{57}Co -labelled vitamin B_{12} was measured by Schilling's (1953) test.

A bromsulphalein excretion test was carried out after rapid intravenous injection of 5 mg/kg of bromsulphalein. Gastric secretion was studied by the technique of Lambing and Bernier (1964). Biopsy of the small intestine was carried out by mouth, using a hydraulic biopsy tube (Debray, Cerf, and Cherbuy, 1966). The samples were examined first using a binocular lens, then under the light microscope.

Blood serotonin was determined by the method of Matray and Moreau (1964), blood histamine by the method of Code (1937). Blood bradykinin was assayed

by the method of Oates, Pettinger, and Doctor (1966) in case 2, and by the method of Webster and Gilmore (1965) in case 3. Blood prostaglandins were assayed by the method of Von Euler and Eliasson (1967).

RESULTS

The chronological relationship between the course of the diarrhoea and that of the tumour are summarized in Table I. On three occasions the tumour appeared, sometimes a long time before, the diarrhoea. In two patients (cases 3 and 4) diarrhoea occurred a short time before the discovery of lymph nodes or bony metastases. In the third patient (case 5) the tumour was large when diarrhoea occurred. However, in case 1, in which diarrhoea preceded the discovery of the tumour by one year, the latter was still only small. In this case, complete surgical removal of the lesions appeared to cause the diarrhoea to disappear immediately, and the patient remains apparently well four years later. In the second patient (case 2) an incomplete surgical removal, leaving in place the left cervical lymph nodes, caused only a short remission of the diarrhoea.

Diarrhoea was maximal from the start in three patients (cases 1, 2, and 4). On two occasions (cases 3 and 5) it increased progressively, and was

roughly proportional to the size of the tumour or its metastases.

In Tables II to IV are summarized the clinical and paraclinical characteristics of the diarrhoea during the patients' periods in hospital.

The number and the average weight of the stools were 2 to 12 and 500 to 700 g per 24 hours respectively. Defaecation was irresistible, after meals and sometimes during the night, and was preceded by abdominal colic in case 2. Although diarrhoea had usually been present for a long time (from 10 months to 10 years), the general condition of the patients was satisfactory apart from a constant loss of weight (5.5 to 25 kg).

The stools were liquid and their water content varied between 85% and 93.1%. They sometimes contained visible vegetable fibres and in every case examination under the microscope showed large quantities of digestible cellulose and intra- and extracellular starch. The daily weight of faecal fat was normal or slightly increased. The sodium content was increased in every case, and the potassium content was increased in four cases out of five (Table II).

Absorption of D-xylose was normal in the three cases studied. Glucose tolerance tests showed a maximal increase of blood sugar slightly higher than normal in two cases and frankly paradiabetic in

TABLE I

CHRONOLOGICAL RELATIONSHIP BETWEEN DIARRHOEA AND THYROID TUMOUR

Case No.	Sex	Age at		Mode of Onset of Diarrhoea	State of Tumour at Investigation of Diarrhoea	Duration of Diarrhoea at Time of Investigation	Flush	Parathyroid Adenoma, Pheochromocytoma, Neuroma, Cushing's Syndrome
		Discovery of Tumour	Onset of Diarrhoea					
1	M	50	49	Rapid	Nodule in thyroid right, left cervical lymphadenopathy	1 yr	0	0
2	F	8	8	Rapid	Retrooccipital lymphadenopathy, multiple pulmonary metastases	10 yr	+	0
3	M	34	50	Gradual (1 yr)	Residual right cervical lymphadenopathy, liver metastasis	4 yr	0	0
4	M	37	55	Rapid	Nodule of thyroid right lobe, bony metastases	10 mth	0	0
5	M	11	34	Gradual (4 yr)	Large thyroid tumour, diffuse cervical lymphadenopathy	7 yr	0	0

TABLE II

STOOL ANALYSIS

	Case No.					
	Normal	1	2	3	4	5
Day		7	5	10	10	3
Weight (g/24 hr)	150 ± 50	580	500	700	650	540
Faecal fat (g/24 hr)	<6	—	7.8	2.4	11	2.7
Cellulose	0	++	++	++	++	+
Starch	±	++	++	++	++	++
Bilirubin	—	+	—	+	—	—
Water (%)	78	85	87.6	92.7	93.1	9.21
Chloride (m-equiv/24 hr)	<5	17	11.7	13.1	—	17.2
Sodium (m-equiv/24 hr)	5	36	32.8	45.1	31	36.3
Potassium (m-equiv/24 hr)	8 to 12	33	33.4	27.4	15.1	31.3

TABLE III
INTESTINAL FUNCTION TESTS
Case No.

	Normal	1	2	3	4	5
Maximum increase of blood sugar after an oral load of 50 (g/l)	> 0.3 ≤ 0.6	0.7	1.7	0.7	0.8	1.05
Intravenous glucose tolerance test (%)	> 1	1.41	1.15	1.45	1.45	0.77
k factor (%)	< 2					
Xylose test (25 g)	6 g ± 2 (5 H)	—	6.1	7.6	—	4.5
Schilling test (%)	> 10	—	12.3	32.8	—	21.7
Action of codeine and codethyline on diarrhoea	—	—	Cured	Cured	—	Cured

three cases. In the three latter cases the coefficient of glucose assimilation after intravenous injection was normal in two cases and less than 1% in only one case. The Schilling test was normal in the three cases studied (Table III).

Laboratory investigations to determine the metabolic effects of diarrhoea included estimation of serum proteins, serum albumin, blood electrolytes, blood lipids and total cholesterol, and haemoglobin. These were nearly all within normal limits.

The overall duration of transit through the gut as measured by noting the colour of the stools after swallowing a red carmine tablet was constantly shortened, and was between three and a quarter and eight and a quarter hours. A radiological study after swallowing a small quantity of barium confirmed the increased rate of transit in both small and large intestines. Barium reached the caecum within an hour and two and a half hours, and the rectum between one and a half and four hours, but the barium swallowed remained fragmented and a significant quantity of barium was noted to be still in the stomach and duodenum when the rectum was already opacified. Furthermore, radiological investigations showed the absence of organic lesions of the digestive tract (Table IV).

Peritoneoscopy in case 3 allowed the direct observation, in the small bowel, of an abnormally

TABLE IV
MEDULLARY CARCINOMA OF THYROID INTESTINAL TRANSIT TIME

Case	Barium Meal		Total Red Dye
	Small Intestine	Total	
1	1 hr	1 hr 30	3 hr 15
2	1 hr	3 hr 45	8 hr 15
3	2 hr 30	4 hr	6 hr 30
4	1 hr 30	—	—
5	2 hr	2 hr 30	5 hr
Normal	4 hr	18 hr	18 hr

high number of contracting rings and their frequent progression as peristaltic waves.

Peroral biopsy of the small intestine at various levels showed in two cases partial villous atrophy, in patches, with a moderate inflammatory reaction, and in the third case a normal mucosa and submucosa. In no case was there any abnormality of the epithelium. Staining with Congo red did not bring to light any amyloid material in the walls of the vessels.

The results of titration of substances acting on smooth muscle and their metabolites carried out in the blood and urine are set out in Table V. The serotonin level was increased in case 2 but not significantly. A search for prostaglandin activity in the systemic blood in case 3 gave only trace values and was negative in case 2. Finally, examination

TABLE V
ESTIMATIONS OF SUBSTANCES ACTIVE ON SMOOTH MUSCLE
Case No.

	Normal Values	2	3	5
<i>Urine</i>				
5 HIAA (mg/24h)	3-8	2.1	1.0	4.4
Amino-acids paper chromatography		Normal	Normal	Normal
V.M.A. (mg/24h)	3-6	3.5	4.0	5.0
<i>Blood Serotonin (μg/ml)</i>				
(a) Systemic: before adrenalin	0.2-0.5	0.92	0.45	
after 10 μg adrenalin		0.77	0.49	
(b) Venous: ¹ before adrenalin	+ ²	0.80		
after 10 μg adrenalin	+ ²	0.65		
<i>Blood Bradykinin (ng/ml)</i>				
(a) Systemic: before adrenalin	0.2-0.7	0.30	0.75	
after 10 μg adrenalin		0.30	0.80	
(b) Venous: ¹ before adrenalin	+ ²	0.40		
after 10 mg adrenalin	+ ²	0.45		
<i>Prostaglandins in Arterial Blood</i>				
	0	0	Trace	

¹Blood from the right brachiocephalic vein.

²To be compared with arterial blood values. Significantly higher values would have been evidence for secretion by the tumour.

under the fluorescent microscope, after exposing the frozen tissue sections to formol vapours, did not show, in case 2, any fluorescence in the neoplastic cells.

DISCUSSION

The frequency of the finding of chronic diarrhoea during medullary carcinoma of the thyroid was 29.3% in William's series (1966) and 28.3% in the series of Ibanez *et al* (1967) which included 41 and 51 cases respectively.

There is a good deal of evidence in favour of the hypothesis that a disorder of transit through the gut is the main cause of diarrhoea in our cases: the urgent desire to pass a motion just after meals or during the night; the presence in the stools of large quantities of cellulose and starch, and sometimes of bilirubin; the very rapid appearance of carmine red dye in the stools after its ingestion; and the spectacular disappearance of diarrhoea under codeine and codethyline, which are known to decrease intestinal motility. It must be emphasized that the radiological studies showed the barium meal passing very rapidly through both the small and the large intestine. Hypermotility of the small bowel, moreover, was confirmed by direct examination during a peritoneoscopy in case 3. Our radiological findings are in agreement with the experience of other authors (Williams, 1966; Cope and Williams, 1967) as well as the activity of codeine on the diarrhoea (Cope and Williams, 1967).

On the other hand, peroral biopsies showed a normal or mildly impaired small intestinal mucosa in our three cases where such a study was done. Thus, the investigations of the intestinal function of patients suffering from a medullary carcinoma with diarrhoea afforded an opportunity of studying the consequences on intestinal absorption of hypermotility of the whole bowel.

The main components of faecal losses in our cases appeared to be water and electrolytes. Steatorrhoea was mild or absent. Xylose and Schilling tests were normal in the three patients studied. The absence of malabsorption of fat, xylose, and vitamin B₁₂ was also noted in cases reported by other authors (Cope and Williams, 1967; Moertel, Beahrs, Woolner, and Tyce, 1965; Bayless, 1967) with the exception of the case 2 of Schimke, Hartmann, Prout, and Rimoin (1968). Moreover, oral glucose tolerance tests gave paradiabetic curves in four of our five cases. But the K factor, as determined by an intravenous glucose tolerance test, was normal in all cases but one. This discrepancy may be interpreted as the consequence of an increased rate of glucose absorption, as in certain patients following gastrec-

tomy (de Lact and Vandenbrouche, 1951): hypermotility in the small bowel, instead of the absence of the pylorus after gastrectomy, could lead to the glucose solution flooding the intestine, so increasing the surface of the absorptive area.

Our cases provide little information concerning the mechanism of the disorder of intestinal motility. The relationship between carcinoma and the increased rate of transit is demonstrated in case 1 where the diarrhoea disappeared completely and immediately after the removal of the tumour. This fact was also observed in several other reported cases (Williams, 1966; Ibanez *et al*, 1967; Davis, 1967). Williams (1966) emphasized the correlation between the size of the tumour and the existence of diarrhoea (Bayless, 1967) and suggested the secretion of a humoral factor.

Flushing occurred in case 2 and in certain other published cases (Williams, 1966; Ibanez *et al*, 1967; Moertel *et al*, 1965). The presence of serotonin (Falck, Larson, Mecklenburg, Rosengren, and Svenaus, 1964) or the possibility of an uptake of 5-hydroxytryptophan and its conversion into serotonin (Pearse quoted by Cope and Williams, 1967) have been demonstrated in the parafollicular thyroid cells of several animal species. These facts led us to seek, during medullary carcinoma with diarrhoea, hypersecretion of vasoactive excitomotor substances analogous to those found in the carcinoid syndrome. Our results were, on the whole, negative except for a mild increase in plasma serotonin in one case. This is also true of the cases published by other authors. The only positive results were those in one case of Moertel *et al* (1965), two cases of Cope and Williams (1967), and one case of Ibanez *et al* (1967) which concerned serotonin and its derivatives, and one case of Williams where kallikrein was demonstrated in the tumour. As far as Ljungberg's discovery of fluorescence after exposure of the tumour to formol vapours is concerned (Jungberg, Cederquist, and Von Studnitz, 1967), this has not been confirmed by other authors (Meyer and Abdel-Bari, 1968) nor in our case 2 (Hillemand *et al*, 1967).

Williams, Karim, and Sandler (1968) recently demonstrated the presence of appreciable amounts of prostaglandins E₂ and F₂ and in tumour tissue from four of seven cases of medullary carcinoma of the thyroid, with or without diarrhoea. Raised systemic blood levels were detected in two cases with diarrhoea; concentration was considerably lower in peripheral venous blood than in blood draining the tumour; nevertheless, systemic concentrations reached levels which are known to be physiologically active on intestinal smooth muscle. Systemic blood prostaglandin assay gave a faintly positive result in one of our cases, but was negative in another.

High thyrocalcitonin-like activity has been demonstrated in blood and tumour extracts from patients with medullary carcinoma of the thyroid (Meyer and Abdel-Bari, 1968; Milhaud, Tubiana, Parmentier, and Coutris, 1968; Cunliffe, Black, Hall, Johnston, Hudgson, Shuster, Gudmundsson, Joplin, Williams, Woodhouse, Galante, and MacIntyre, 1968; Tashjian and Melvin, 1968). Increased thyrocalcitonin-like activity was shown in the peripheral venous blood of our cases 5 (Milhaud *et al*, 1968) and 3 (Hioco, Rambaud, Miravet, Dryll, Prost, and Bernier, 1968) and recently in our case 2. But thyrocalcitonin does not seem to have any stimulating effect on gut motility.

The presence in certain medullary carcinomas of the thyroid of a hypertrophy or of neurofibroma of the Auerbach and Meissner plexuses of the intestinal tract (Schimke *et al*, 1968) could be in some way related to the disturbance of gut motility. Finally, as suggested by Williams *et al* (1968), it appears that several agents may act synergistically to cause diarrhoea associated with medullary carcinoma of the thyroid.

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