Current Practice

Treatment of Thyroid Cancer

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Three hundred and one patients with thyroid cancer have been treated under my supervision at New End Hospital and at the Royal Northern Hospital in London and in private practice during the years 1945 to 1966. I have chosen for consideration the patients seen between 1945 and 1963 who have died, who have survived under observation with undifferentiated cancer for five years or more, or have survived under observation with differentiated cancer for 10 years or more. This is the method proposed by the Union International Centre le Cancer, but a five-year "cut-off period" has been added. These cases number 151, distributed as in Table I. The classification used has been that of Warren and Meissner,¹ but I have not distinguished between papillary and follicular carcinomata. Very few of my patients harboured either in a pure form, the majority showing a mixture of the two in every proportion. The sections were all examined by a pathologist as well as by myself. Whenever there was disagreement about the malignancy of a growth the patient was excluded from the series unless subsequent events confirmed the malignancy.

TABLE I

	Dead	Alive after 10 Years	Total
Differentiated carcinoma:			
Papillary or follicular	22	74	96
Graham's tumour	1	2	3
Medullary	5	1	6
Hürthle-cell	3	4	7
Fetal	0	1	1
		Alive after 5 Years	
Undifferentiated carcinoma:			
Small-cell	3	1	4
Giant-cell	11	1	12
Sarcoma:			
Spindle-cell	2	0	2
Reticulum-cell	16	1	17
Leiomyosarcoma	1	0	1
Fibrosarcoma	1	0	1
		Alive	
Mixed papillary and undifferentiated carcinoma	0	1	1
Total	65	86	151

Only 20 patients were "lost." They are probably alive, as their deaths have not been registered, but they have not been included in the series.

Methods

Owing to changing views over the years the methods of treatment were various. These were thyroidectomy, total or subtotal, ¹³¹I, and x rays, alone or in different combinations. The surgical method has been described by Piercy,² most of the operations having been performed by him or by Mr. M. J.

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Lange, whose technique is identical. That of the other surgeons who operated on a minority of the patients does not significantly differ. The radioactive isotope used in every case was ¹³¹I. In earlier cases mathematical formulae were used to calculate the dose, but it was soon realized that these contributed nothing to the results. Most cases were thenceforward treated with approximately 100 mCi.

Pathological Diagnosis

Graham's Tumour.—Three cases were seen. According to Warren and Meissner¹ the prognosis is good and no treatment is necessary other than the original excision. This advice was followed. Two patients were alive and well 15 and 16 years after operation. One died from an unrelated cause four years after operation.

Fetal Carcinoma.—Only one case was seen. The history suggested early irradiation of tuberculous glands as a possible cause. She remains well 14 years after partial thyroidectomy only, though vascular invasion was present at the time of operation.

Hürthle-cell Carcinoma.—Seven cases were seen. Four patients are alive—two at 11 and 13 years, without recurrence after total thyroidectomy. Two of them had a partial thyroidectomy only and are alive at 12 and 20 years. Of the latter, two had invasion of the capsule and of blood vessels at the time of operation but have had no recurrence since; one had no invasion at the time of operation but has since had metastases, treated three times by surgery. Three patients have died; one with very advanced disease died rapidly after total thyroidectomy, one at four years after partial thyroidectomy and deep radiation, and one at 11 years of an unrelated cause, having had no metastases.

Small-cell Carcinoma.—Four cases were seen. One was inoperable and died rapidly of her disease. The other three were treated by nearly total thyroidectomy; of these, two died rapidly without further treatment and one is alive and well at seven years after a "total" thyroidectomy followed by deep radiation. This case is worth noting in view of the difference of opinion about the value of the latter treatment, but the very bad prognosis in such cases is confirmed. Perhaps the "total" thyroidectomy was indeed total and the irradiation irrelevant.

Giant-cell Carcinoma.—Twelve cases were seen. Of these patients one, a very early case, is alive and well 12 years after a partial thyroidectomy followed by ¹³¹I. Perhaps the whole growth was by good fortune removed. Four patients were in extremis when first seen and received only palliative treatment. One died of carcinoma six years after a total thyroidectomy and radiation. One whose growth was inoperable had x-ray treatment unavailingly. The remaining five died rapidly despite attempted total thyroidectomy followed by x rays.

Medullary Carcinoma.—Six cases were seen. One was inoperable and died of carcinoma in two months. One treated

by total thyroidectomy and x rays died of carcinoma in a few months. One treated by partial thyroidectomy, x rays, and ^{131}I is alive and well at 10 years. Of the other three, treated by total thyroidectomy and x rays, one died soon after operation of a cause that is not known, the other two of coronary infarction after a few months and after nine years respectively. The high proportion of deaths from coronary disease may be interesting. None of the six had the associated diseases described, phaeochromocytoma, diarrhoea, or tumours of mucous membranes. The patient who is alive and well at 10 years had involvement of lymph nodes at the time of operation.

Mixed Carcinoma.—The one patient seen, a woman of 23, is worthy of description. In 1952 she complained of a goitre present for three months. A biopsy having confirmed the presence of carcinoma, a nearly total thyroidectomy was carried out. The microscopical section showed almost all types of malignant change, papillary, follicular, and solid undifferentiated small-cell carcinoma. She was given x-ray therapy, which was followed by a severe reaction. A small area of residual tissue having been located by scanning, an ablation dose of ^{131}I was given. Apart from a transient right Horner's syndrome she remained well, taking 0.3 mg. of thyroxine daily, until July 1967, when she became severely dyspnoeic and dysphagic. Tracheostomy and gastrostomy were necessary. When last seen in May 1968 she was able to breathe normally when she occluded the tracheostomy and could swallow normally again. Scar tissue, due to reaction to radiotherapy, severely limited her neck movements, but no signs of carcinoma could be detected. She now has a left Horner's syndrome, the right side being normal.

Sarcoma.—One case of fibrosarcoma, one of leiomyosarcoma, and two of spindle-cell sarcoma were seen. They were inoperable and the patients died rapidly despite x-ray therapy. Seventeen cases of reticulum-cell sarcoma were seen; of these five were already in extremis. In the other 12 total thyroidectomy was impossible, and in some a biopsy only could be carried out. They were treated by x rays, but, despite rapid and sometimes dramatic improvement, nine were dead within a year. Two, however, survived for nine years and died of unrelated causes, and one is alive and well at 13 years.

Papillary and Follicular Carcinoma.—Ninety-six cases were seen, and the number perhaps warrants tabulation (Table II). As stated above, it was found impossible to separate altogether the papillary and follicular groups. They overlap too much. Nevertheless, there is a possibility that, as reported by several

TABLE II.—Papillary and Follicular Carcinoma

Treatment	No.	Alive	Dead	Percentage Alive at 10 Years
T	22	18	4	82
T+I	18	16	2	88
T+X+I ..	3	1	2	66
P	22	15	7	68
P+I	19	16	3	84
P+X	5	3	2	60
P+X+I ..	5	3	2	60
X	1	0	1	0
O	1	0	1	0

T = Total thyroidectomy alone. P = Partial thyroidectomy alone. I = ^{131}I . X = Deep irradiation. O = No treatment.

authors, there may be a relation between the amount of follicular tissue and the response to ^{131}I therapy. Whatever method of treatment was adopted the results were good. The lower rate of success when deep irradiation was used is probably explained by the employment of this measure only in the most severe cases. There seems to be little evidence in these figures to suggest that the use of ^{131}I affects the ultimate issue when the primary treatment is total thyroidectomy, the success rate being raised by 6% only. However, when the primary treatment is partial thyroidectomy only (sometimes because a total operation was impossible, sometimes because secondary operation was refused or considered to be inadvisable), the success rate rises by 16%.

Discussion

Use of X Rays.—The use of x rays in the treatment of thyroid carcinoma has been much debated. In this series it was used as set out in Table III. This shows a depressing picture. One is bound to suspect that the solitary patient alive after total thyroidectomy and x-ray therapy for giant-cell carcinoma would have survived after surgery alone. The results in sarcoma are more encouraging. Certainly the short-term results are brilliant, the growth melting often like snow in sunshine. Maybe the long-term results are capable of improvement.

TABLE III.—Results of External Irradiation

	No. of Cases	Alive at 5 Years or Over
Small-cell carcinoma	1	1 at 7 years
Giant-cell carcinoma	7	1*
Fibrosarcoma	1	0
Leiomyosarcoma	1	0
Reticulum-cell sarcoma	12	3 at 9, 9, 13 years
Medullary carcinoma	4	1 at 10 years
Mixed carcinoma	1	1 at 16 years
Hürthle-cell carcinoma	1	0

* Died at six years.

The significance of metastases or local spread appears to have been overrated. Of the 96 patients with follicular or papillary carcinoma in this series, 60 had metastases that were detected before or during operation or invasion of the capsule or blood vessels. Of these, 48 are alive and well at 10 years or more (80%). Of the 36 who had no detectable malignant spread 28 are alive (78%). The effect of metastases occurring later is more serious; but of 43 patients, 26 (60%) have survived, sometimes after numerous such incidents. Of the 55 who had no such recurrences, 49 (89%) have survived. This may be an argument in favour of node dissection, which was not usually carried out in the series under review.

Age of Onset.—It has often been suggested that the earlier the age of onset the better the prognosis. Table IV seems to bear this out. Despite the disparity manifest in the twenties, it seems clear that the risk of death is greater if the disease occurs in middle age. It is possible that the good prognosis in the very young is explained by the fact that the tumours are almost always of the follicular and papillary variety, the prognosis of which is so good at any age. As Beregi *et al.*⁸ pointed out, and as I have confirmed, even invasion does not imply a bad prognosis. Crile and Hazard⁴ go so far as to suggest that any type of tumour is less malignant in the young, a point supported by my example of undifferentiated carcinoma in a woman of 23 who after total thyroidectomy and other possibly irrelevant treatment remains well 17 years later. A girl of 9 who came in 1956 with extensive secondaries in the lungs and cervical nodes and was treated by total thyroidectomy and radioactive iodine is today alive and well with no evidence of any recurrence.

TABLE IV.—Age at Diagnosis Related to Result of Treatment of Follicular and Papillary Carcinoma

	Age at Diagnosis									Total
	< 10	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	
Alive at 10 years	1	8	9	18	18	14	7	5		80
Dead of cancer			4		2	7	4	2	1	20
Dead of unrelated causes ..						1	2	2		5

Sex.—Mustacchi and Cutler^{5,6} have found that cancer of the thyroid progresses five times as fast in males as in females. My own figures are insufficient for any conclusion to be drawn except in the follicular and papillary group. Of 21 males, 8 died of carcinoma (38%), whereas of 74 females 12 died of that disease (16%). The conclusion that the prognosis is worse in males is supported by this series.

Conclusions

Three hundred and one patients with malignant disease of the thyroid have been treated under my supervision in the period 1945 to 1966. Of these, 151 who have died or have survived under observation for at least five years (in the case of undifferentiated carcinoma) or 10 years (in that of differentiated carcinoma) are considered. Treatment has been by various combinations of total and partial thyroidectomy, radioactive iodine and deep x-ray therapy. Except in papillary and follicular carcinoma, the numbers involved are insufficient for a valid comparison of the results of treatment, but tentative conclusions are probably justifiable.

1. Papillary and follicular carcinoma is of relatively low malignancy and the majority of patients survive for 10 or more years whatever treatment is adopted. After total thyroidectomy the advantage of secondary treatment with radioactive iodine is doubtful, but it seems to be of real value after partial thyroidectomy.

2. Deep x rays have a very small part in the treatment of carcinoma of the thyroid of any type, though benefit may occasionally accrue. The results in reticulum-cell sarcoma appear to be better.

3. The initial presence of metastases or of invasion of the capsule or blood vessels does not affect the prognosis in patients who receive adequate treatment.

4. The later appearance of metastases has an adverse but not tragic effect on the prognosis.

5. The age at which the diagnosis is made is significant. It is an advantage if the disease occurs before the age of 50.

6. The prognosis in males is worse than that in females.

Most of the surgical operations were carried out by Mr. J. E. Piercy and Mr. M. J. Lange at New End Hospital, a smaller number by Mr. R. S. Murley at the Royal Northern Hospital. Treatment by radioactive iodine and x rays was in most cases carried out by Dr. A. W. G. Goolden and Miss Helen Farran at New End Hospital, and a smaller number by Mr. Anthony Green at the Royal Northern Hospital. The pathologists concerned were Dr. A. B. Bratton, the late Dr. S. Robinson, and Dr. Michael Peters. To all of these collaborators I tender my thanks, as well as to the Registrar General for help in the follow-up and to Mr. Michael Curwen for statistical advice.

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TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in common use.

Changing Oral Contraceptives

In 1962 doubts began to be raised that oral contraceptives increased the risk of thromboembolism, and a close watch has been kept for this possibility. Evidence has been accumulating that oestrogens given alone increase the risk of thrombosis. The Committee on Safety of Drugs has now warned that there is a greater risk for women taking oral contraceptives containing more than 50 µg. of oestrogen, and advised that such products should not normally be prescribed. Many doctors will accept this evidence and want to advise women about changing products before the full figures are published.

Changing from a high- to a low-dose oestrogen oral contraceptive could entail increased chance of pregnancy and the development of side-effects which are more common with low-dose products.

Mode of Contraceptive Action

The progestogens used belong to two groups: (1) 19-nortestosterone derivatives—norethynodrel, norethisterone and its acetate, lynestrenol, ethynodiol diacetate, and norgestrel, (2) 17-alpha-hydroxy progesterone derivatives—chlormadinone and megestrol acetate.

These compounds have varying degrees of potency in inhibiting ovulation by blocking release of luteinizing hormone and producing progestational, oestrogenic, antioestrogenic, androgenic, glucocorticoid, and anabolic effects.

The oestrogens used are ethinyloestradiol (E.O.) and ethinyl-oestradiol 3-methyl ether (mestranol). Mestranol is converted to ethinyloestradiol in the body, but whether the two drugs have different biological effects in some women is not clear at present.

Oestrogens inhibit ovulation by inhibiting release of follicle-stimulating hormone¹ but produce a dose-related response—a small dose is stimulating, a borderline dose may delay ovulation—and it seems that for British women a dose of 100 µg. of either ethinyloestradiol or mestranol is required to ensure adequate inhibition of ovulation. Even with this dose an occasional pregnancy may result, and with lower doses the rate becomes higher. Mears² found pregnancy rates of 5% with sequentials containing 80 µg. of mestranol and 20% with sequentials containing 50 µg. of ethinyloestradiol. The higher doses of oestrogen (75 µg. and 100 µg.) produce higher levels of urinary oestrogen than are found in the normal cycle.

Classification

The Table shows oral contraceptives classified according to oestrogen dose and hormone balance with the incidence of break-through bleeding (B.T.B.).

Hormone Balance of Some Oral Contraceptives with % Incidence Break-through Bleeding in First Year

	50 µg. Oestrogen or no Oestrogen	More Than 50 µg. Oestrogen
Strongly progestogenic	Anovlar 21 2% Gynovlar 21 3%	Metrolen 2% Lyndiol 2% Ortho-Novin 2 mg. 2%
Intermediate	Norlestrin } 6% Minovlar } Orlest 28 } Volidan } 10% Norinyl-1 }	Ovulen } 4% Lyndiol 2-5 } Ovanon } Nuvacon 12% Demulen 15% Conovid 16% Conovid E 16% Previcon
Oestrogenic sequential (pregnancy rate 0-5%)		Serial 28 0.5% Sequens 4% C-Quens 1% Feminor 21 1%
Low dose progestogen (pregnancy rate 1-12%)	Verton, Normenon 23%	