FIG. 5.—Pre-operative (a) and post-operative (b) rectal biopsies.

which were not responding to medical treatment the colon containing the vast bulk of the disease was to be excised, then the cause of the gross toxæmia would be removed and with the consequent return of the patient to good health the inflammatory changes in the residual rectum might well resolve.

If the toxæmia was to be overcome it seemed essential that the whole of the colon, including the pelvic colon, should be excised, as clinical and pathological examination of many specimens of the disease had shown that the distal regions were often the most heavily affected. Should a lesser excision be undertaken it appeared likely that ill-health associated with the presence of a segment of the pelvic colon might well continue in a considerable proportion of the cases, so that resolution of the inflammation would not take place. The whole of the colon was therefore excised in the cases in this series and ileo-rectal anastomosis carried out, and we believe that the resolution of the inflammation in the remaining rectum that has taken place in all but three of the patients is dependent upon this total excision.

All patients have been repeatedly examined in the follow-up department and have been examined by a narrow-bore proctoscope. The mucosa appears to have regenerated in all except the three cases referred to. As a result of fibrosis the rectum will not distend as will a normal rectum, which is the reason for the use of a proctoscope with a smaller lumen. The mucosa, too, appears fixed to the underlying structures and has not the mobility of the normal rectal lining.

To record this resolution of the inflammatory change we have in many of the cases taken a rectal biopsy before and after operation, and the healing suggested by macroscopic examination has been confirmed to have taken place by the pathological examination of these specimens (Fig. 5).

It is therefore established that, following total colectomy and ileo-rectal anastomosis, resolution of the residual inflam-

mation in the rectum can occur, but, as will be seen from the sections, the normal pattern of palisaded glandular formation is only partially regained.

Should the Disease Persist or Recur in the Remaining Rectum can the Latter be Removed and an Ileostomy Established Without Risk?

No case has been converted to a permanent ileostomy, as the indications for this have not arisen in the present series. It would seem, however, that the conversion would not present any great surgical problem.

Summary

A series of 47 cases of diffuse ulcerative colitis treated by total colectomy and ileo-rectal anastomosis is analysed.

It is concluded that the operation can be carried out with a low mortality rate and low post-operative morbidity, and that 70% of the patients return to a normal economic and social life and a further 15% have only minor limitations, the result of some frequency of bowel action.

It is suggested that the procedure described should be the primary method of choice in the surgery of diffuse ulcerative colitis.

[Since the completion of this article several months ago the residual rectal ulceration in the two cases treated by intra-cavitary ultra-violet light has resolved. These patients could now be included in the first category.]

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SIMPLIFIED RADIOACTIVE IODINE THERAPY

BY

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The treatment of thyrotoxicosis with radioactive iodine (^{131}I) is now an established procedure for the management of selected patients.

The long-term experience of one of the pioneer groups of American workers has been reported (Chapman and Maloof, 1955), and Myant (1956) has reviewed the results achieved throughout the world from 1942 to 1954. In this country the most extensive reported experience has been that of Blomfield, Jones, Macgregor, Miller, Wayne, and Weetch (1955), who reviewed results in the first 140 patients treated in Sheffield.

Varying techniques have been used to obtain consistent and satisfactory results. Some workers attempt to simulate partial thyroidectomy by achieving remission in as many patients as possible by a single treatment with the isotope (Blomfield, Jones, Macgregor, Miller, and Wayne, 1951; Freedberg, Kurland, Chamovitz, and Ureles, 1952; Fraser, Abbatt, and Stewart, 1954; Chapman and Maloof, 1955). Others give small and repeated doses of the isotope, preferring to treat the patient gradually and slowly, hoping thereby to minimize the likelihood of producing myxoedema (Williams, Towery, Jaffe, Rogers, and Tagnon, 1949).

Whatever technique is adopted, however, the prime consideration is that when the dose is prescribed for an individual patient the need for an early remission of symptoms is balanced against the likelihood of producing eventual myxoedema (Myant and Pochin, 1955).

Any technique which attempts to cure the patient quickly and effectively by a single treatment with ^{131}I involves the selection of a dose thought to be optimal in terms of ^{131}I concentration in the thyroid gland (Chapman and Maloof, 1955; Fraser *et al.*, 1954) or of radiation dosage in rads delivered to the thyroid (Blomfield *et al.*, 1951; Freedberg *et al.*, 1952). The calculations necessary to determine these doses are complicated (Myant and Pochin, 1955), and depend upon a number of assumptions that are not always valid.

This paper is a preliminary account of the experience of one observer who endeavoured to employ a precise and quantitative technique for a number of years (Blomfield *et al.*, 1955) and then, as a result of the experience gained, followed thereafter a different and, by previously accepted standards, completely heretical technique. The results are reported on the first 150 consecutive cases so treated after a minimum observation period of one year.

Principles Involved in Dosage Prediction

Any attempt to use a predetermined dosage of radiation in terms of rads or of ^{131}I concentration makes a number of assumptions the validity of which is doubtful.

(1) It is assumed that the dose of radiation is delivered uniformly throughout the gland. It has, however, been shown (Kelsey, Haines, and Keating, 1949) that there is an uneven distribution of ^{131}I in the thyroid gland. Oddie (1951) has moreover calculated that, even where a uniform concentration throughout the gland is assumed, there could theoretically be a hundredfold difference between the highest and lowest dosage received within any one gland. So, at best, any prediction of dose concentration is no more than an inaccurate mean value.

(2) The variable factors required to calculate the radiation dosage are the peak percentage uptake of the isotope by the gland, the effective half-life of the isotope in the gland, and the mass of the gland itself. For the calculated dosage to have any meaning these preliminary measurements must be exact, and although uptake and half-life can be defined accurately there is no sure method of assessing thyroid gland mass. Soley, Miller, and Foreman (1949) accepted that the mass, as judged by inspection and palpation, might be inaccurate by as much as 30 to 40%. Many attempts have been made to devise objective techniques, such as that of Blomfield *et al.* (1953), by which gland volume may be calculated. Measurements can be made in two planes with a collimated Geiger or scintillation counter, but even such techniques cannot be dissociated from a possible subjective bias by the observer. Kelly (1954) found that there might be very large errors inherent in similar and even more refined methods. Gland size is undoubtedly the most important factor in dose determination, and its accurate calculation is essential if doses are to be expressed either in rads or in microcuries per gramme of thyroid tissue. If a figure is applied to an estimate of gland mass it may acquire undue significance, and on subsequent review it is easy to forget the fictitious accuracy of the original estimate. The false precision of many of the calculations previously performed in relation to isotope therapy has often deluded the protagonists of such calculations that they have a value in excess of their real worth.

(3) Predetermined dosage techniques require that the metabolism of the ^{131}I be similar following both the tracer investigation and the therapeutic dose. Uptake measurements are usually in reasonable agreement, but Blomfield *et al.* (1951, 1953) and Freedberg *et al.* (1952) found

occasional alterations in effective half-life. The biological elimination of the isotope from the gland was often shorter after treatment, presumably owing to an early release of hormone as a result of radiation damage. Table I demonstrates

TABLE I.—Comparison of Predicted and Measured Radiation Doses (rep)

Case No.	Predicted from Tracer Measurements	Measured after Therapy
1	8,000	8,600
2	10,800	13,500
3	7,900	7,500
4	8,700	8,300
5	9,000	5,600
6	8,000	7,300
7	11,000	11,800
8	6,200	6,200
9	8,500	11,300
10	8,000	7,300

strates the sort of variation in dosage that may ensue, and the calculated radiation dose delivered is thus significantly different from that originally planned. In this series of 10 cases, originally discussed by Blomfield *et al.* (1953), the actual dose delivered in Cases 2, 5, and 9 is appreciably different from that envisaged. The same gland size was used in the estimation of both doses, and the variations in these cases were chiefly due to differing effective half-lives. Miller and Sheline (1951) also found a very wide range of values for the actual dose delivered to the patient. When they "pre-selected" a dose of 6,000 reps (roentgen-equivalent physical) the doses actually delivered varied from 2,000 to 20,000 reps.

(4) The use of a predetermined dose schedule assumes that the biological response to a given dose of radiation or concentration of ^{131}I is constant and predictable. This is certainly not the case. The radiosensitivity of different glands is a biological variable. This results in some patients being inadequately treated with a dose which has delivered perhaps three times as much radiation as that which has rendered another patient myxoedematous. The accompanying Figure (from Blomfield *et al.*, 1955) illustrates the relationship between the clinical result and the calculated rad dosage, although some of this apparent variability may be due to errors in estimation of gland size. It can be seen that some patients remained toxic after doses of more than 10,000 rads, whereas others were made myxoedematous with less than 4,000 rads. A similar lack of correlation between clinical result and the actual dosage of radiation delivered was shown by Miller and Sheline (1951). Myant (1956) has fully discussed the factors which may be partly responsible for these results, but, making all possible allowances, it is apparent that such a degree of biological variability renders dose prediction impracticable.

Alternative Therapeutic Techniques

It is apparent that precise calculation of ^{131}I concentration in the gland demands an accurate knowledge of gland mass, and this is not easy to ascertain. The technique involving dosage fractionation by means of the repeated administration of small doses of ^{131}I involves numerous measurements of thyroid function. These may be of prognostic value (Myant, 1953), but the inevitable time-lag before treatment is complete makes the method unsatisfactory and inconvenient for patient and physician.

Relationship of rad dosage delivered to the thyroid gland to the clinical result, after the first treatment with radioactive iodine (from Blomfield *et al.*, 1955).

Alternatively, the disease can be treated more simply by adjusting the dose in millicuries to that most likely to effect a rapid clinical cure while avoiding as far as possible the development of myxoedema. An attempt has therefore been made to treat patients on these lines, without considering the details of uptake measurements and without attempting to assign a figure in grammes to the size of any given thyroid gland.

Method Used

Patients judged suitable for ^{131}I therapy by criteria defined previously (Blomfield *et al.*, 1955) were given a preliminary tracer dose of ^{131}I . This confirmed the diagnosis and ensured that the thyroid gland was able to absorb a high proportion of the administered dose. The criteria of toxicity were those of Goodwin, Macgregor, Miller, Wayne (1951) and Fraser, Hobson, Arnott, and Emery (1953).

Patients who lived within a reasonable distance from hospital were treated as out-patients, and comparatively few required to be admitted. ^{131}I was then given, the size of the dose being judged on the simple principle of a small dose for a patient with a small gland and a large dose for a patient with a large gland. Past experience had shown that myxoedema was seldom produced by doses as low as 5 millicuries even where gland enlargement was minimal. Chapman and Maloof (1955) have since shown that among 520 patients the smallest single dose to produce myxoedema was 6 millicuries. Our practice was to give 4 millicuries to patients in whom the thyroid was impalpable, 5 or 6 millicuries for minimally enlarged glands, and increasing doses up to the highest single dose of 15 millicuries, which was given to a patient with a large nodular gland. Other factors besides that of gland mass also influenced the size of dose prescribed: for example, larger doses were given to patients with significant cardiac failure, if the gland was nodular, or if the need to obtain a rapid remission of symptoms was greater than the risk of the production of hypothyroidism.

A few of the most thyrotoxic patients received a course of carbimazole before ^{131}I , but normally no preliminary treatment of this nature was prescribed. In such cases, however, the principles governing the prescription of the dose remained unaltered, and the ^{131}I was given after the administration of the antithyroid drug had been stopped for at least four days and after the tracer-dose investigation had been completed. If it was thought advisable to diminish the patient's toxicity before the effect of the ^{131}I therapy had had time to develop, a course of potassium iodide, 60 mg. daily, was given, starting not earlier than one week after the ^{131}I had been given, and continuing for not longer than three weeks. On general principles it was felt undesirable to give antithyroid drugs after ^{131}I therapy, but this was in fact done on a few occasions as a preliminary to further isotope treatment.

Patients were normally seen six weeks after treatment, and thereafter at successively longer intervals. If, however, there was no clinical improvement after six to ten weeks, it was our custom to arrange for a further tracer-dose investigation and for the administration of additional ^{131}I . The same principles governed the size of dose prescribed. Many patients who have been inadequately treated experience appreciable shrinkage of the thyroid gland, and this may determine that a smaller dose should be used on a subsequent occasion.

Results

We are here concerned only in reporting these initial results so that this technique may be compared with the more elaborate methods previously employed. It is not intended to detail the sequence of recovery and complications which ensues after ^{131}I therapy, as this has been fully discussed elsewhere (Blomfield *et al.*, 1955; Myant, 1956).

Between January 1, 1953, and October 31, 1956, 267 patients were treated by this technique. Table II summarizes the results in the first 150 consecutive patients followed for a minimum period of one year after they were first treated.

TABLE II.—*Clinical Results of Radioactive Iodine Therapy (Minimum Follow-up, One Year)*

	Result of First Treatment				Clinical State after 12-46 Months	
	Patients		Dose (mc.)		Patients	
	No.	%	Mean	Range	No.	%
<i>Present Series (150 Patients)</i>						
Euthyroid ..	89	59	8.0	4-15	130 (3 dead)	87
Still toxic ..	48	32	8.4	6-12	3 (2 dead)	2
Hypothyroid ..	13	9	7.9	4-10	17 (1 dead)	11
<i>Blomfield et al. (1955) (140 Patients)</i>						
Euthyroid ..	—	62	9.6	2.4-22.4	—	84
Still toxic ..	—	27	12.2	4.0-31.6	—	4
Hypothyroid ..	—	11	9.2	5.2-15.9	—	12

At the time of follow up 87% of the patients had been rendered euthyroid; 11% had become hypothyroid and were receiving thyroxine maintenance treatment; and 2% (3 patients) had either died while still thyrotoxic or required further treatment. Fifty-nine per cent. of the patients were rendered euthyroid, and 9% became myxoedematous after their first dose of the isotope.

Of the 48 patients (32%) who required more than one treatment, 41 later became euthyroid; of these, 28 required two, 11 required three, and 2 required four therapeutic doses. Four of these 48 patients became myxoedematous after their second treatment. Of these four, two were made hypothyroid intentionally because of associated intractable cardiac failure.

Two patients died within a year of receiving ^{131}I . One died as a result of long-standing portal hypertension, but, although improved, she was still thyrotoxic at the time of death despite having been treated on three occasions. The other was a woman aged 70 who died a few days after her second treatment. She fell heavily while in hospital and fractured the neck of her femur; fatal hypostatic pneumonia ensued. A third patient was still toxic after one year, but became euthyroid following further treatment.

Apart from the two patients who died while still thyrotoxic, four others had succumbed by the time the review was made (November 1, 1956). Three were elderly men who had been rendered euthyroid and who later had myocardial infarctions. The fourth was a patient with advanced diabetic nephropathy who died in uraemia two and a half years after severe hyperthyroidism had been adequately controlled.

Table II also includes for comparison the corresponding percentage figures for the 140 patients reported by Blomfield *et al.* (1955), who had been treated by a method of dose selection involving an elaborate and quantitative technique. It can be seen that the results in Edinburgh were essentially similar and the differences between the two groups are insignificant. The range of doses in millicuries employed in both centres is roughly comparable, but the mean figures are slightly lower in Edinburgh.

Discussion

The results achieved with this simple clinical technique are in no way different from those previously obtained when the prescription of the dose was governed by more meticulous and elaborate methods. Furthermore, they are essentially the same as have been reported by other centres. The four patients who became myxoedematous after a second therapeutic dose were all among the first 60 who received treatment. The production of hypothyroidism in this way can usually be avoided if sufficient patience is exercised and the physician is prepared to wait for the late remission that sometimes occurs. Nevertheless, our experience coincides with that of Myant (1956), who found that if no improvement has occurred after 10 weeks further therapy is almost invariably necessary.

If it is confirmed that similar or better results can be obtained by the use of this technique, ^{131}I therapy could be

greatly extended. The principles are essentially so simple that there is no reason why other physicians should not achieve the same results even if they have not previously had the advantage of experience with more meticulous methods. It is important that tracer-dose investigations should always precede ^{131}I therapy, because they confirm the diagnosis, and ensure that the uptake of ^{131}I by the thyroid gland is high. Failing such tests it is inevitable that mistakes in diagnosis and management will occur.

The majority of patients who receive ^{131}I therapy would in the absence of the isotope be treated by partial thyroidectomy. This operation, including the pre-operative preparation and recovery, usually involves at least three weeks in hospital, with all the expense to the National Health Service that such an admission entails. Thereafter a shorter or longer period of convalescence is necessary before the resumption of ordinary activities. When patients are treated with ^{131}I in hospital they need not remain for longer than three or four days unless their general condition warrants it. Treatment of out-patients, on the other hand, involves no expense except that of the isotope itself. This is trivial in comparison with the costs of the hospital admission. Including transport charges, an average dose of 8 millicuries costs less than £2. The economies effected by isotope therapy are therefore considerable.

The elaborate methods previously used in an attempt to determine precisely the dose to be prescribed are expensive. The detailed measurements necessary, particularly when gland size is estimated by scanning techniques, involve physicists and technicians in an expenditure of time and effort probably unjustified by any advantage which accrues.

From the long-term point of view it is important that some centres with adequate facilities, and a sufficient staff of physicists and technicians, should continue to make quantitative observations upon the amount of radiation delivered in isotope therapy. Only then can further knowledge be obtained about the factors responsible for the variation in response. Effective and safe treatment, however, can be carried out at any centre with a minimum of equipment and technical personnel. The cases here reported have been treated by one physician with the assistance of a single technician. It therefore should not be thought that the application of radioactive iodine in the treatment of thyrotoxicosis is necessarily a complex procedure.

Summary

A series of 150 consecutive cases of thyrotoxicosis have been treated with radioactive iodine. A simple clinical dosage technique has been used, based primarily upon an approximate estimate, by inspection and palpation, of thyroid gland mass, although certain other clinical factors were also taken into consideration.

On review after a minimum period of one year, 87% of patients had become euthyroid, 11% were myxoedematous, and 2% had been inadequately treated. Fifty-nine per cent. of the patients were satisfactorily treated with a single dose of the isotope.

The results achieved did not differ appreciably from those previously reported in which a method had been employed for dose selection involving an elaborate and quantitative technique.

The prescription of an entirely accurate radiation dose is impracticable, chiefly because of the errors inherent in the techniques for the estimation of gland mass, and because of the biological variability in the radiosensitivity of different glands. Elaborate techniques are unnecessary for the safe and effective treatment of thyrotoxic patients.

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DANGEROUS BLEEDING ASSOCIATED WITH CARCINOMA OF PROSTATE

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Excessive bleeding sometimes develops in patients with metastatic carcinoma of the prostate. The bleeding may occur either spontaneously or in association with surgical procedures, especially those directly involving the malignant prostate. Bleeding of varying degree may arise from any site, particularly the urinary tract and the nose, and in the skin as ecchymoses. If surgery is performed dangerous bleeding may take place into the traumatized area. Scott (1956) reports the loss of 1.5 litres of blood into the scrotum following orchidectomy in such a case. The haemorrhage may be severe enough to cause death if properly directed treatment is not given.

The relationship between bleeding and carcinoma of the prostate has not been fully explained. Recent studies of abnormal clotting have shown, however, that in certain cases of metastatic carcinoma of the prostate the phenomenon of fibrinolysis develops and that this is associated at times with a drop in the level of plasma fibrinogen (Tagnon *et al.*, 1953a, 1953b). Such fibrinolysis is thought to be due to proteolytic enzymes which dissolve away blood clot by digesting fibrin (fibrinolysis), in some cases also lysing fibrinogen (fibrinogenolysis) and other clotting factors such as prothrombin and factor V. Tagnon *et al.* (1953b) have demonstrated an abnormal fibrinolysin in the blood of 12% of their patients with metastatic carcinoma of the prostate, and