JOURNAL OF NUCLEAR MEDICINE 8:515-528, 1967

306 Cases of Toxic Adenoma: Clinical Aspects, Findings in Radioiodine Diagnostics, Radiochromatography and Histology; Results of ^{131}I and Surgical Treatment[1]

W. Horst,[2] H. Rösler, C. Schneider, and A. Labhart

Zürich

Hyperthyroidism has no uniform etiology. Of three patients, only two fit the picture of the syndrome described first by Graves and later, in more detail, by Basedow. The third patient's hyperthyroidism is caused by a toxic adenoma.

The diagnosis of toxic adenoma is possibly only by means of a specialized radioiodine study. We offered from our experiences in Hamburg, Germany, 1953, a clear-cut distinction between toxic adenoma and Graves' disease by means of scanning and certain routinely performed radioiodine functional investigations (1, 2). This method has been practised by the same team since 1963 in Zürich. This survey, therefore, can compare results from the North Sea coastal regions of Germany with those from Swiss regions at the foot of the alps. It becomes evident, therefore, that toxic adenoma is a frequent condition in goitrous regions as well as in districts without endemic goiters.

This differentiation has its most important consequences in treatment of hyperthyroidism. The particular treatment of toxic adenoma—whether by surgery or with radioiodine—is quite different from that of Graves' disease. Iodine-131 treatment of toxic adenoma does not entail appreciable risk, early or late, of myxedema and surgical treatment is also particularly free of such risks.

On the other hand, radiochromatography of urine and serum does not show qualitative differences in the ^{131}I-containing compounds in normal controls, Graves' disease and toxic adenoma, although there are quantitative differences.

---

[1]Presented at the Fifth International Thyroid Conference, Rome, 1965.

[2]Universitätsklinik für Radiotherapie und Nuklearmedizin, Kantonsspital, Zürich/Schweiz.

METHODS

Our routine radioiodine study is characterized by uptake measurements and scanning before and after administration of TSH and before and after administration of thyroid hormone (1, 2). The ^{131}I-uptake in the thyroid region is measured after two and 48 hours and the ^{131}PBI evaluated after 48 hours. This proceeding, which was first described by Horst in 1953 (1, 2) and is still unchanged, is the basis for diagnosis of toxic adenoma today. Additional examinations are resin-^{131}I-T_3-uptake measurement and analysis of ^{127}PBI. Scans, sometimes presented in color, are performed with electronic background subtraction (3) and count-print translation linear from lowest to highest count rates over the thyroid gland. Cut off and other non-linear delineating systems are strictly avoided, because they are the main source of error, particularly where the diagnosis is missed.

A hot or warm nodule in the scanned thyroid region is suspicious of toxic adenoma, but not all these nodules are toxic adenomata. We have to assess the accelerated production of thyroid hormone, independently of the pituitary, within this nodule.

The first example in the upper row in Figure 1 shows scintigraphic findings in what we call a decompensated toxic adenoma. First, radioiodine is taken up only in a circumscribed region, namely in the adenoma itself. The thyroid gland, on the other hand, is not to be seen in this scan. After administration of thyrotropic hormone (1) (TSH) to this patient, one finds the scintigram above right. Now not only the adenoma but also the thyroid can be seen.

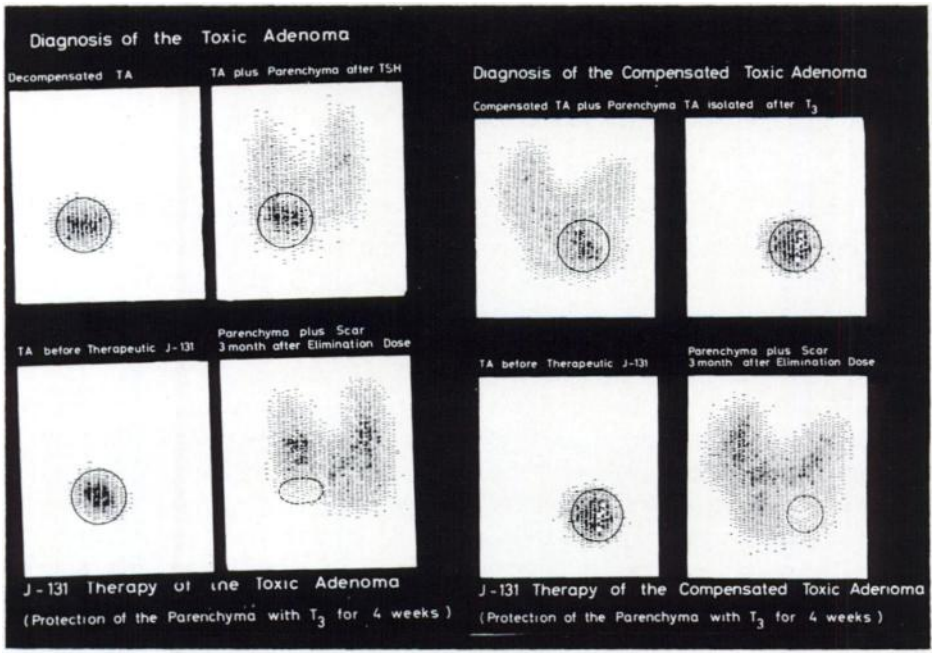

Fig. 1 (left). Diagnosis of the toxic adenoma (Copies of color scans).
Fig. 2 (right). Diagnosis of the compensated toxic adenoma (Copies of color scans).

A warm nodule within a still active thyroid gland is the first scintigraphic finding in the case of a compensated toxic adenoma. (Figure 2, above left). After oral administration of T_4 or triiodothyronin (1,2) the healthy parenchyma is inactivated. In this stage of examination only the toxic adenoma takes up iodine-131 (above right). In the first example, only the perinodular tissue could be stimulated by additional TSH administration; in the second one, the radioiodine uptake could be suppressed within the perinodular tissue only by additional T_4 or T_3 administration, in other words, by lowering of the endogenous TSH level. In both cases, the perinodular thyroid tissue follows the rules of thyroid-pituitary regulation. On the contrary, uptake (and metabolism) of iodine in the nodule is independent of thyrotropic hormone; its function is autonomous.

These effects upon the thyroid-pituitary axis make it seem probable that the substance produced within the nodule must be thyroid hormone. From here we are entitled to give the name "toxic adenoma" to this circumscribed tumor of the thyroid gland.

In the first example, autonomous hormone production within this adenoma was sufficient to suppress radioiodine uptake by the perinodular tissue (Figure 3); mechanisms of regulation in the thyroid-pituitary axis are ruled out now. We call it the decompensated stage of the TA. In the second example, there is still small scope for such regulation; we call this stage the compensated one. (1, 2, 11).

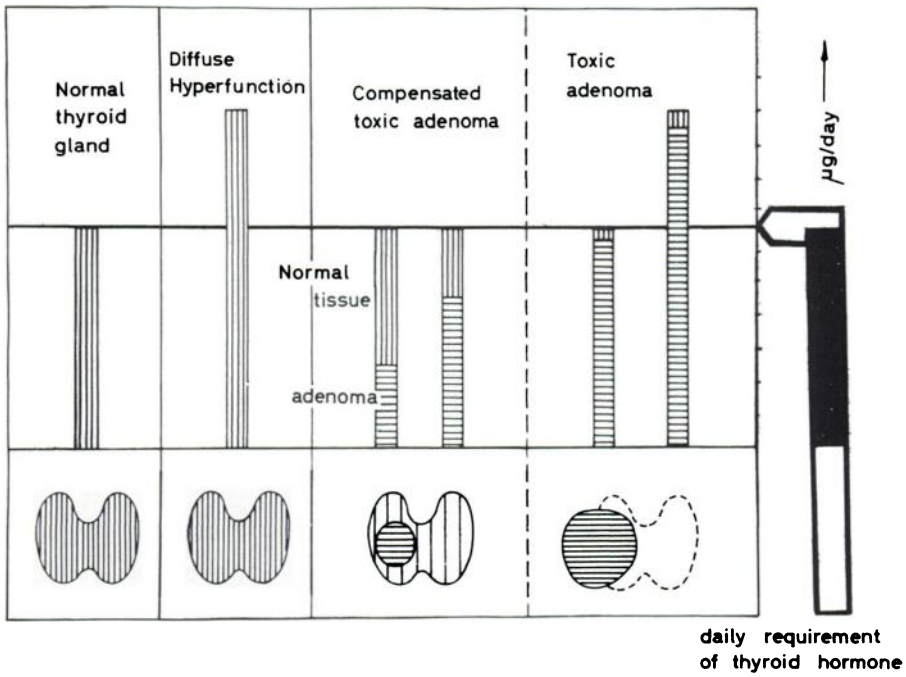

Fig. 3. Definition of compensated and decompensated toxic adenoma in comparison to normal and diffuse hyperfunctioning thyroid.

Compensated and decompensated toxic adenoma are different stages of the same disease (Fig. 4). Compensated toxic adenoma develops slowly into a decompensated adenoma. This development can be documented; the average weight of the compensated toxic adenoma as determined from scanning is 19,2 ± 2,7 (n = 63); that of the decompensated toxic adenoma, on the other hand, is 40,5 ± 3.0 g (n = 211). The 48 hours' ^{131}PBI rises from 0,74 ± 0,13%/l to 1,37 ± 0,11%/l, corresponding to the increase in clinical symptoms.

RESULTS

Three hundred and six patients with toxic adenoma were examined, treated and followed up by the same team under standardized techniques. Half of these patients were seen in Hamburg (156), while the others were seen in Zürich, Switzerland. When first examined, 232 of these toxic adenomata cases were in the decompensated stage. Only 74 patients, that is approximately 25%, had a compensated toxic adenoma. Table I contains these numbers in detail.

Findings of the ^{131}I-three-phase study, completed by the addition of the average values for the ^{127}PBI, are summarized in Table II. The ^{131}I uptake in the thyroid region, 2 hours and 48 hours after ^{131}I administration, is indeed raised in comparison to the normal controls, but not to the same degree as in Graves' disease. The deciding factor in the diagnosis is above all the ^{131}PBI in the 48-hour serum, which is raised, as in Graves' disease. The resin-^{131}I-T_3-uptake is also raised to slightly higher values than normal; they fall, however, between the normal values and those for Graves' disease.

In 180 normal controls, the values for two hours' uptake lay between 10% and 30% and the value for the ^{131}I in the 48 hours-serum between 0,01% and 0,24%/l (1). In Survey Table III, the number of cases of toxic adenoma are given in which these values fell into the normal range.

The accuracy of both determinations is less limited with decompensated toxic adenoma. The rate of error of 3,6% for the 48 hours ^{131}PBI-determination in the case of the decompensated toxic adenoma and of 18% in the case of the compensated toxic adenoma makes these determinations the most important after the scintigraphic examination.

TABLE I

TOTAL NUMBER OF TOXIC ADENOMATA IN THIS SURVEY

	Hamburg	*Zürich*	*Hamburg u. Zürich*
Toxic Adenoma decompensated	105	127	232
Toxic Adenoma compensated	51	23	74
Total	156	150	306

The raised value for the ^{131}PBI in the 48-hour serum is the expression for the accelerated iodine turnover and the increased hormone secretion rate within the toxic adenoma. This value can also be manifested in a progressive

Autonomous Toxic Adenoma of the Thyroid Transitional Stages of Toxic Adenoma		
	 compensated	decompensated
Total of Clinical Symptoms	73 % →	93 %
Heat Intolerance Palpitation, Weigt Loss	6 % →	23 %
Weight of Adenoma	19 g →	41 g
Serum PBI^{131}/liter after 48 hr	0,7 % →	1,4 %
	63 cases	211 cases

Fig. 4. Transitional stages of the toxic adenoma.

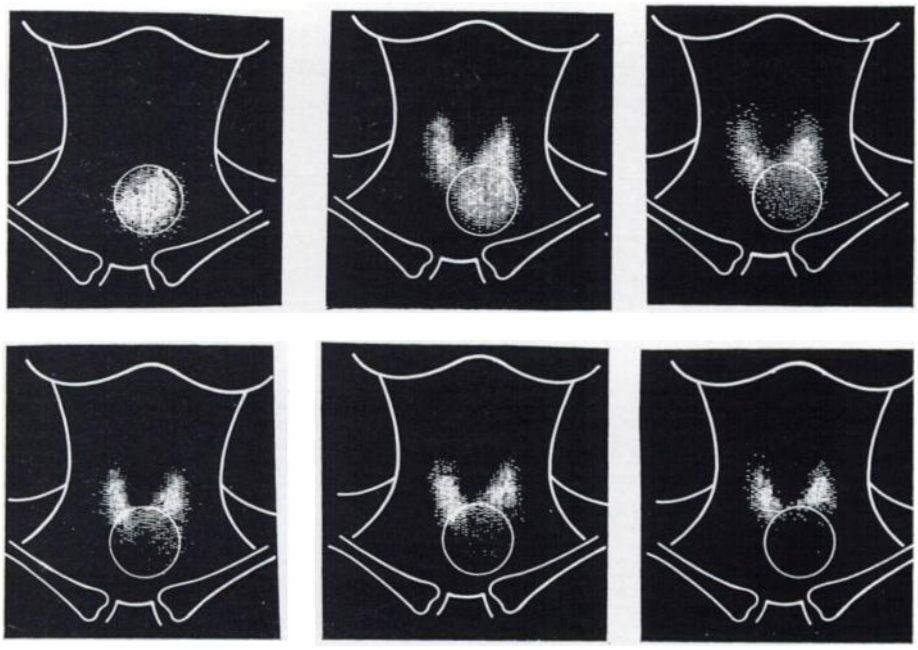

Fig. 5. Scintigraphic course of a toxic adenoma ("Leakage Phenomenon").

series of scintigraphic examinations, as Fig. 5 shows. After TSH administration, the toxic adenoma is to be seen as a warm nodule within the typically configurated thyroid gland (2nd picture above). Within 14 days, this adenoma has become a cold nodule within the thyroid gland (figure below right). The TSH-activated thyroid tissue binds the ^{131}I with longer half-time than the nodule does.

This "leakage-phenomenon" (6) is seen not only in the case of an autonomous toxic adenoma, but is also found in the rare "non-autonomous adenoma with accelerated iodine turnover." This rather rare condition may be accompanied clinically by euthyrodism or hyperthyroid symptoms. The synopsis of differential diagnosis of the warm and the hot thyroid nodule (Fig. 6) takes into consideration, therefore, not only the findings of the radioiodine function study, but also the progress as shown in the scintigraphic examinations (5).

RADIOPAPERCHROMATOGRAPHY

Paperchromatographic examinations of serum and urine were performed after administration of ^{131}I in the following groups: controls with normal thyroid function, toxic adenoma and Graves' disease. Extracts were separated mostly in a butanol-ammoniac-dioxan system.

In the serum of all three groups were found: T_3, T_4, iodide and traces of iodotyrosines. We never found any atypical ^{131}I-containing substances. On chromatographic separation of the urine butanol extract, we found a number of unidentifiable ^{131}I-containing substances. Here, too, we did not find any atypical spots in comparison with Graves' disease and normal controls in the chromatogram in the case of toxic adenoma (Fig. 7). The chromatograms were evaluated both quantitatively and by autoradiography. All spots in front of the iodide fraction with RF—values up to 0,43—were taken as FO ("organic fraction"). If we integrate the area of this FO-fraction and express it as a ratio of

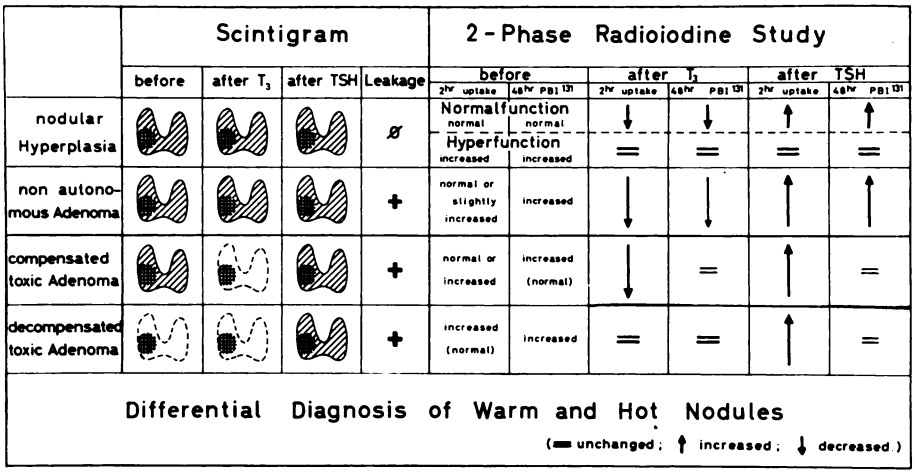

Fig. 6. Differential diagnosis of warm and hot nodules.

the ^{131}I-T_3, which is found in very large quantities in the urine, this ratio varies typically within the three groups. During the first few hours after administration of ^{131}I, this ratio is, in Graves' disease, three to six times as high as in toxic adenoma and is also much higher in euthyroid controls than in toxic adenomas. This FO-fraction lies in the lowest range in the case of the toxic adenoma (Fig. 8). We can assume that precursors in the hormone synthesis are running with this FO fraction, their concentration in the urine depending on the degree of thyrotropic stimulation of the parenchyma (4).

The results of radiochromatographic examinations of the serum are demonstrated in Figure 8. There seems to be no difference in the decrease of ratio ^{131}I-T_3 to ^{131}I-T_4, when toxic adenoma and diffuse hyperfunction are compared (Fig. 9).

CLINICAL FINDINGS

Clinical findings are also able to demonstrate some peculiar characteristics of the toxic adenoma in contrast to the diffuse thyroid hyperfunction. The frequency distribution shows a majority of the diffuse thyroid hyperfunction over the toxic adenoma in clinical material. Of 453 thyrotoxic patients seen in Zürich, (one year collection), 328 had a diffuse thyroid hyperfunction and 125 had a toxic adenoma; that is, one third of all cases in Zürich examined or treated because of a thyrotoxicosis had a toxic adenoma. These numbers correspond with our results from Hamburg (5).

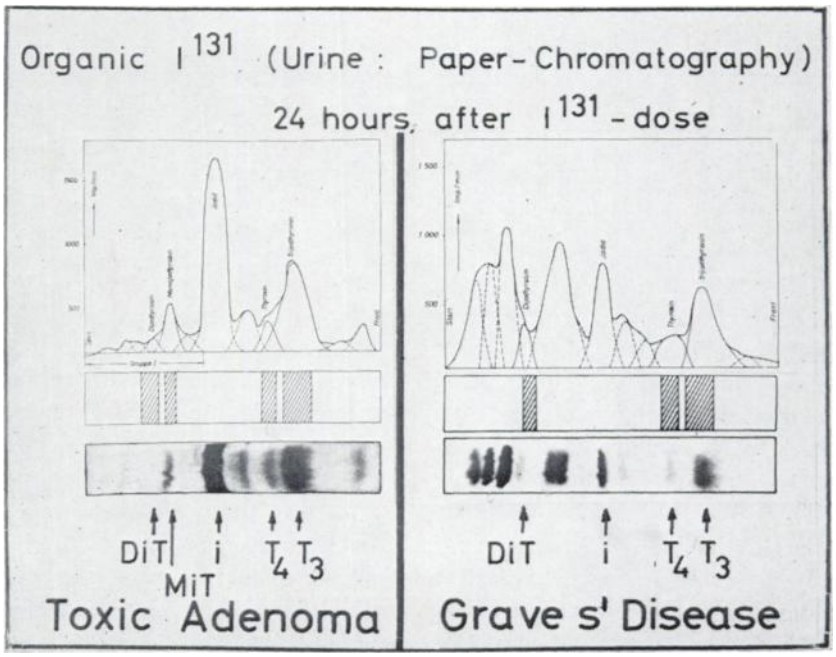

Fig. 7. Radiochromatography of the butanol-extract of urine, comparison between toxic adenoma and Graves' disease.

The history of Graves' disease is usually short, averaging anywhere from 2.6 ± 0.04 years; on the other hand, in the case of toxic adenoma, it is often difficult even to determine the starting point of the disease (5.3 ± 0.88 years). The toxic adenoma probably develops as a benign tumour, usually slowly growing. The appearance of clinical symptoms is slow and there is no sign of a sudden or even dramatic onset of development, as one sees in Graves' disease. The protracted development of thyrotoxicosis in the case of a toxic adenoma allows a progressive adaption of the patient to his disease. However, 72% of the patients complain of excitability and 56% of palpitation, which are therefore guiding clinical symptoms in those with toxic adenoma. In addition, heat intolerance (41%), loss of weight (25%), and more rarely diarrhoea (10%) are reported. The sex distribution is notably similar to that in the case of Graves' disease. Women predominate with 5.8 : 1 over men (306 analyzed cases from Hamburg and Zürich). Among 910 patients with diffuse hyperthyroidism, the ratio is 6:1 : 1, as against 2.1 : 1 in 192 patients with euthyroid goitre. Similar agreement can be found in the reports of thyroid diseases within the patient's family (based on first degree relatives only): 29.5% positive in case of the toxic adenoma, 26.8% in Graves' disease, but 58% in euthyroid goitre.

By simple neck palpation, 72% of the toxic adenomata presented as a uninodular goitre (150 unselected patients with toxic adenoma were analysed). Uninodular enlargement was palpated in only 18% of the cases with a diffuse thyroid hyperfunction. One often finds a toxic adenoma within a multinodular goitre (25% as against 21% in Graves' disease), but more rarely in a case of no palpable goitre or in a case of diffuse parenchymatic thyroid enlargement (3% as against 61% in Graves' disease).

Eye symptoms with exophthalmus were never found in patients with toxic adenoma, but were distinct in 35% of the cases with Graves' disease and present in altogether 52% of our patients with this condition. The combination of uninodular goitre in the absence of exophthalmus points to a toxic adenoma as the 80% probable cause of the hyperthyroidism, as calculated from Table II.

TREATMENT OF THE TOXIC ADENOMA

Since toxic adenoma can be diagnosed by *in vivo* examinations, (i.e. since toxic adenoma is not a histological diagnosis), an operation is not the treatment *"sine qua non."* As a rule, toxic adenoma is eliminated with radioiodine. Where the nodule shows an extremely accelerated iodine metabolism, the operation is to be preferred, as it leads to a more rapid cure. Surgical treatment has a better cosmetic effect in cases with considerable regressive alterations (7, 8, 9).

We look back on 273 patients (124 from Hamburg, 149 from Zürich), who could be followed-up for at least 10 months and up to 12 years after treatment. Over two-thirds of all cases were treated with ^{131}I and a bare one-third surgically.

Radioiodine dose is calculated in Roentgen-equivalents for the toxic adenoma and aims for destruction of the entire adenoma. The surrounding parenchyma, inactive or inactivated by exogenous administration of T_3 before ther-

apy, is protected after administration of the therapeutic dose against re-utilized radioiodine for a further two to four weeks by continued triiodothyronine administration (5, 6).

In the first example (Fig. 1) the radioiodine treatment of a decompensated toxic adenoma is demonstrated. After confirmation of the diagnosis with control-scan after TSH (upper row right), one must wait until up to three weeks later, the decompensated stage is spontaneously re-established (lower row, left). Then the therapeutic dose is given. The healthy thyroid tissue is then protected by T_3-medication for a further two to four weeks. Three months later, we see the fourth picture; in the region of the former adenoma, only scar tissue is now palpable. Here radioiodine is no longer taken up. On the other hand, the paranodular thyroid tissue takes up ^{131}I spontaneously.

The primarily compensated toxic adenoma is treated by radio-iodine after administration of T_3 (Fig. 2). The destruction of this adenoma proceeds, as before, under protection of the healthy thyroid tissue with T_3 administration for two to four weeks, too (below left). Three months after therapy, a scar results in place of the former warm nodule (Fig. 2, below right).

The aim of the operation is exclusively the enucleation of the adenoma, while carefully sparing the healthy atrophic thyroid tissue; ligation of the thyroid vessels should be avoided (7, 8, 9).

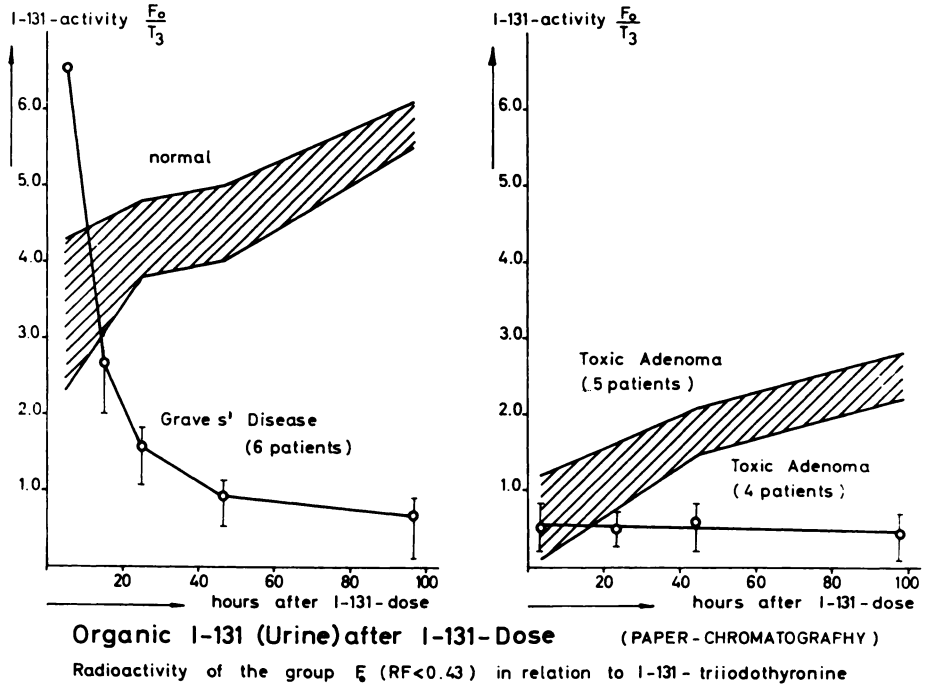

Fig. 8. Variation of the ratio "Organic Fraction" to T_3 in the urine with time (toxic adenoma and Graves' disease).

SUCCESS AND RISKS OF THERAPY

A total of 81 patients (Zürich) was treated with varying doses per adenoma. Only results of control-examinations, three months later will be considered. Fifty-four patients were clinically cured and 26 improved. Only one patient's condition was unchanged (Table IV). The higher the elimination dose was chosen, the better the result: 83% cured after 30,000 rads and higher doses as against 48% after doses lower than 20,000 rads/adenoma. The only unchanged patient received 15,000 rads/adenoma.

Follow-up scintigrams already showed in the majority of cases after three months and in the others rather later, the typical thyroid figure. Here, too, we found the result dependent on the elimination dose. A scar, that is, no radioiodine uptake in a nodule reduced in size or no palpable nodule at all, was found in half of the patients (16 out of 30) treated with 30,000 rads and higher, but only in 2 patients out of 28, treated with doses lower than 20,000 rads. In a further 38 out of all 81 patients concerned, there was a residual ^{131}I uptake in the nodule, but the perinodular tissue was reactivated spontaneously and a compensated stage of the toxic adenoma was the result, as could be proven by an additional examination after administration of T_3. However, sixteen patients still had a decompensated, but smaller residual toxic adenoma. Low uptake mea-

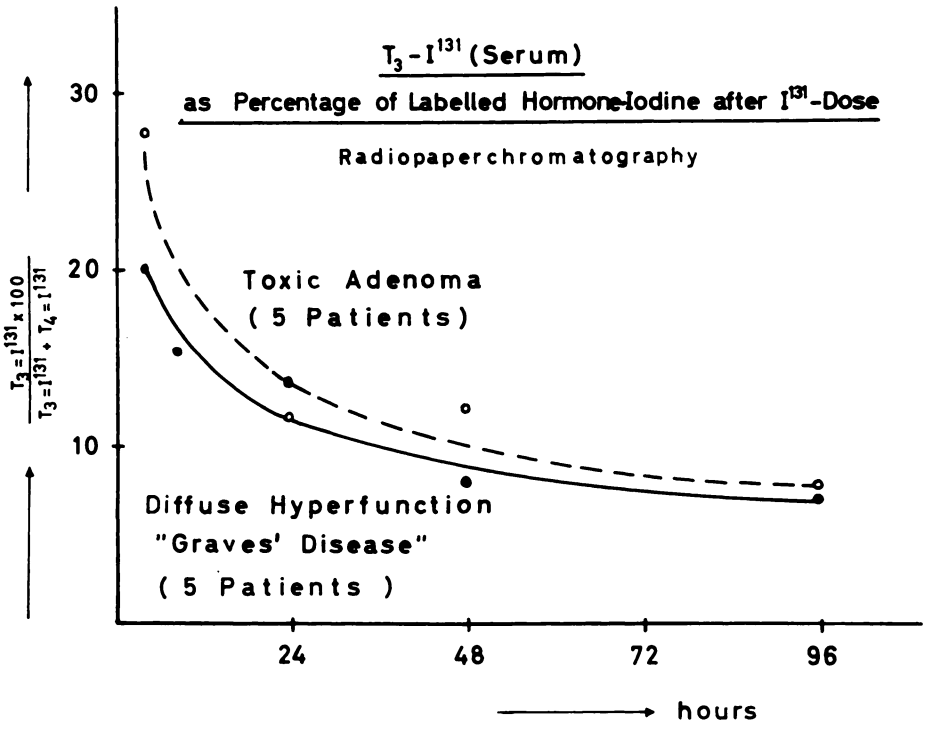

Fig. 9. Variation of the ratio T_3 to T_4 in the serum with time (toxic adenoma and Graves' disease).

surements are typical for these patients. Clinically they are euthyroid, so they do not immediately need any further therapy. We saw spontaneous reanimation of perinodular tissue after several months and these findings corresponded to our observations from Hamburg (4, 5).

The optimal radiation dose lies between 20,000 and 30,000 rads within the toxic adenoma. This treatment entails no risk. In no case was an acute aggravation of the hyperthyroidism seen before the radioiodine took effect. The whole-body dose is in general lower than in the treatment of Graves' disease. In the rare cases not cured (see above) the ^{131}I therapy is repeated. This therapy also is without risk, when the protection of the perinodular tissue by T_3 is strictly adhered to.

The surgical technique described is less risky than subtotal strumectomy, which is necessary in diffuse hyperfunction. Tetanie, paralysis of the recurrens nerve or death during or after operation did not occur in our 79 cases (7, 8, 9).

In none of the 306 cases of autonomous adenoma did we find clinical signs of malignant growth and in 79 cases a histological study was carried out. In Hamburg (Prof. Krauspe) were found follicular (75%), but also trabecular (8%), embryonal (3%) and, even in 14%, papillary adenomas. In Zürich (Prof. Uehlinger) the histological picture was more uniform: eight mainly microfollicular, 11 macrofollicular differentiated adenomas as against five mixed follicular, one microfollicular-trabecular adenoma, as published by Cope, Rawson and Mac Arthur (10).

These different histological results make it clear that the condition is difficult to diagnose by means of morphological criteria. Thyroid parenchyma surrounding the adenoma is atrophied. However, functional atrophy is difficult to distinguish from pressure atrophy, which may also be caused, for example, by

TABLE II

RESULTS OF RADIOIODINE 3-PHASE-STUDY WITH RESIN-I^{131}-T_3-UPTAKE, AND OF PBI^{127} IN TOXIC ADENOMA, COMPARED WITH NORMAL CONTROLS AND GRAVES' DISEASE

(Average ± SD; n = number of cases, diagnosis affirmed by progress after therapy)

	I^{131}–Uptake after 2 hours	*I^{131}–Uptake after 48 hours*	*PBI^{131} $_{48}$hr %/1 Serum*	*Resin–I^{131} T_3–Uptake*	*PBI^{127} µg/100 ml Serum*
Normal Controls	19.0 ± 0.65% (n = 180)	45.0 ± 1.1% (n = 180)	0.08 ± 0.01 (n = 180)	1.0 ± 0.014 (n = 100)	5.5 ± 0.15 (n = 77)
Toxic Adenoma	33.4 ± 1.4% (n = 251)	49.8 ± 1.34% (n = 254)	1.26 ± 0.12 (n = 252)	1.24 ± 0.03 (n = 60)	10.4 ± 0.8 (n = 49)
Graves' Disease	54.8 ± 0.5% (n = 1144)	61.8 ± 0.3% (n = 1144)	1.20 ± 0.02 (n = 1144)	1.46 ± 0.03 (n = 100)	11.7 ± 0.4 (n = 73)

adenomas without hormonal activity. Therefore this criterion, too, is of little value in diagnosis of the toxic adenoma.

LONG-TERM RESULTS AFTER THERAPY: PROGNOSIS

In the case of ^{131}I treatment of Graves' disease, the early and particularly the cumulative risk of myxedema is considerable. In our own material, it was 27% after 10 years, in the literature are found cumulative rates of myxedema after ^{131}I treatment of Graves' disease of up to 36%.

We observed only one myxedema among 194 patients with toxic adenoma after ^{131}I treatment. In this patient, the T_3 protection of the thyroid parenchyma had been missed. Clinical and radioiodine examinations up to 12 years after the start of therapy revealed not one single additional myxedema. Moreover, there was no tendency toward alterations in the direction of hypofunction; that means there was no progressive fall of the uptake values. Behavior after exogenous TSH administration always remained normal. Malignancy occurred, even after many years, in none of our cases. Recurrences were not seen in the radioiodine eliminated toxic adenomas.

Long-term results after surgical treatment were also favorable. Among 79 cases followed-up surgically, we have found up to now only one permanent myxedema. In this case, however, we found, scintigraphically, thyroid parenchyma taking up radioiodine the size of a 30^{gm} residual thyroid gland, which could not be stimulated to sufficient function by administration of TSH.

HYPERTHYROIDISM (SURVEY)

Grave's Disease 2/3	1. Frequency	Toxic Adenoma 1/3
Short case history Rapid progression	2. History	Protracted development
All degrees of severity Triad of Basedow	3. Clinical findings	Mostly mild No endocrine exopthalmus
BMR, PBI, reflextime, J-131: "secondary hyperthyroidism"	4. Diagnosis	J-131: "primary hyperthyroidism"
Therapy of the symptoms: Reduction of hormone production	5. Therapy	Treatment of the cause: Elimination of the TA
Surgical risks Drugs side effects Myxedema-endocrine exophthalmus	6. Therapeutic risks	None! (?)
Incomplete healing (leaving defects) Cumulative myxedema rate Relapse	7. Prognosis	Complete healing No cumulative myxedema rate No relapse! (?)

Fig. 10. Comparison of the clinical features of toxic adenoma and Graves' disease.

Statistics on results of radioiodine treatment of hyperthyroidism must consider the different long-term results of the two different etiological causes. Statistics without this differentiation may be of limited value.

SUMMARY (FIGURE 8)

Toxic adenoma is a frequent occurrence. In about one-third of our cases of hyperthyroidism, an autonomous toxic adenoma was found to be the cause. We found no differences in frequency between patients from coastal regions and those from the forealps, where endemic goitre is a frequent condition.

The diagnosis can only be substantiated by means of a special radioiodine study, namely linear scintigraphy in combination with controls after administration of TSH and T_3.

Chromatography of urine and serum does not show qualitative differences in the ^{131}I-containing compounds in Graves' disease and toxic adenoma; on the other hand, there are quantitative differences.

In the case of toxic adenoma, hyperthyroidism can be cured by permanently removing the cause of hyperthyroidism.

Iodine-131 therapy requires high doses of 20-30,000 rads/toxic adenoma. When carried out under T_3-protection of the healthy parenchyma, there is no early or cumulative risk of myxedema.

The clinical course of toxic adenoma is considerably better than that of Graves' disease, as there is less, in our material practically no risk of myxedema; moreover, there are never complications such as endocrine exophthalmus or circumscribed myxedema.

The histology of the toxic adenoma is not unique and, therefore, is not a basis for diagnosis, but in 79 patients operated and histologically proved, no malignancy was found.

TABLE III

INACCURACY OF I^{131}—UPTAKE—AND PBI^{131} MEASUREMENTS IN TOXIC ADENOMA: RELATIVE NUMBER OF CASES WITH FINDINGS WITHIN THE NORMAL RANGE

	Decompensated Toxic Adenoma ($n = 232$)	*Compensated Toxic Adenoma* ($n = 74$)
2^h—Uptake < 30%	30%	46%
48 h *PBI^{131}* < 0.25%/1	3.6%	18%

TABLE IV

RESULTS OF A SINGLE RADIOIODINE DOSE (3 MONTHS AFTER ADMINISTRATION)—ZÜRICH

Absorbed Dose → *in Adenoma (rad)*	*10'000-19'000*	*20'000-29'000*	*30'000-30'000*	*Total*
Clinically				
cured	14 (48%)	16 (68%)	25 (83%)	54 (67%)
improved	13 (48%)	7 (32%)	5 (17%)	26 (32%)
unchanged	1 (4%)	– (0%)	– (0%)	1 (1%)
Scintigraphically				
Scar	2 (8%)	11 (45%)	16 (52%)	27 (33%)
compensated	16 (55%)	8 (36%)	12 (41%)	38 (47%)
decompensated residual Adenoma	10 (37%)	4 (19%)	2 (7%)	16 (20%)
Number of Patients treated	28 (100%)	23 (100%)	30 (100%)	81 (100%)

ACKNOWLEDGEMENT

We are indebted to Dr. Chapman, Harvard Medical School, Boston, for reading our manuscript and making helpful suggestions and criticisms.

REFERENCES

1. HORST, W.: Verhandl. d. Dtsch. Ges. f. Verdauungs- und Stoffwechselkrankheiten (Stuttgart 1953), S. 152-173.

2. HORST, W.: Sonderband Strahlentherapie 34, S. 150-176 (1954).

3. CONRAD, B. AND HORST, W.: *Medical Radioisotope Scanning*, 1964, IAEA Wien, 1964, S. 491.

4. HORST, W., SCHNEIDER, C. AND THIEMANN, H. J.: Verhandlungen der Deutschen Gesellschaft für Innere Medizin (Wiesbaden 1960) 66, 373-377.

5. HORST, W., RÖSLER, H., SCHNEIDER, C., HEINZEL, F. AND CONRAD, B.: *Radio-Isotope in der Endokrinologie*, Stuttgart, 1965, S. 311.

6. HORST, W.: Sonderband zur Stahlentherapie Nr. 49, S. 6-22 (1961).

7. ZUKSCHWERDT, L. AND HORST, W.: XIXe Congrès de la Société Internationale dé Chirurgie, Transactions, Dublin 1961, S. 210.

8. BAY, V.: Fortschritte der Medizin 1964, S. 577-580.

9. RÖSLER, H., AKOVBIANTZ, A. AND KRAMPF, K.: Helv. Chir. Acta: in press.

10. COPE, O. R., RAWSON, R. W., AND MACARTHUR, J. W.: *Surgery, gynec., obstet.* 84:415 (1947).

11. HORST, W., PETERSEN, J., THIEMANN, H. J., AND ZUKSCHWERDT, L.: *Dtsch. Med. Wchschr.* 85:711-723 (1960).