Fisher for the treatment of dose-response curves in the presence of natural mortality. In our present case the situation is reversed in that instead of a lower asymptote we have an upper one. The method of dealing with this problem statistically is by substituting the residual percentage of Schick positives for the natural "mortality," and then working on the decrease of positives with increasing dosage of toxoid—that is, with a negative regression coefficient. The "maximum likelihood" estimate obtained with Finney's (1949) improved method is $2.7 \pm 0.5\%$ of "non-convertible" children, and the fit of hypothesis obtained by accepting this figure is very good: χ^2 with five degrees of freedom gives a probability of $>50\%$. The curve corresponding to this hypothesis is shown in Fig. 2. Briefly, this analysis suggests, and supports the suggestion, that when an infinite quantity of toxoid is used with 5 or 7.5 mg. of AlPO_4 carrier the maximum S.C.R. obtainable (single dose) is 97.3% ($\pm 0.5\%$ standard error), and when 10 Lf are used the expected S.C.R. will be 96.8% and with 5 Lf 95.25%.

This statistical analysis confirms the conclusions drawn from the simple % S.C.R./dose toxoid curve in that there is a maximum ($<100\%$) S.C.R. for P.T.A.P. The maximum is reached asymptotically, and in such a way that the advantage of using more than 10 Lf per dose is negligible.

Summary

Schick-positive children in the London area aged 1 year were given one intramuscular inoculation (0.5 ml.) of samples of P.T.A.P. containing 10 mg. of AlPO_4 per ml. and decreasing amounts of purified toxoid.

With an inoculation of only 0.5 Lf a S.C.R. of 60% was obtained, and with 5 Lf one of 93.8%.

By employing all relevant data previously obtained, it appeared that a maximum S.C.R. of about 97% was obtainable using a single 5–10 Lf dose, and that this S.C.R. was not exceeded (on the average) if more toxoid were used.

A special statistical examination of all the results also showed that a maximum S.C.R. of $<100\%$ is obtainable with a single inoculation of P.T.A.P. (10 or 15 mg. of AlPO_4 per ml.). Using an infinite quantity of toxoid this maximum S.C.R. was calculated to be $97.3\% \pm 0.5\%$; using 10 Lf per dose, the expected S.C.R. is 96.8%, and with 5 Lf 95.25%.

These maximum conversion rates for a single inoculation are most probably significantly below those following a two-dose method of immunization.

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Dr. Angeliki Tsaona, gynaecologist and obstetrician, and president of the League of Women Scientists of Salonika, is visiting the United Kingdom under the auspices of the British Council. She is studying gynaecological and obstetrical methods in British hospitals, and is particularly interested in the use of anaesthetics in childbirth.

ILL EFFECTS OF THE RADIUM MENOPAUSE*

BY

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Induction of the menopause for non-malignant uterine bleeding is a safe and effective method of treatment, and is much used in the Birmingham School, but the resultant improvement in the patient's health may obscure certain immediate and remote sequelae. In this review attention has been paid to flushing and sweating, loss of libido, and premature senile changes in the genital tract.

In all, 118 cases were examined at an average interval of two years after receiving intrauterine radium (2,400 mg.-hours). The ages of the patients varied from 33 to 58 (average 45). The outstanding symptom after irradiation was flushing, and the cases were grouped according to the following definitions:

(a) *Mild Flushing* (commonest).—An occasional sensation of heat and sometimes sweating with an obvious flush of the face and neck. Normal duties are not disturbed and the patient is seldom inconvenienced.

(b) *Moderately Severe Flushing*.—From 12 to 20 or more flushes by day severe enough to cause temporarily listlessness and a sense of fatigue. Generalized sweating usually accompanies flushing, and this often causes the patient to waken from sleep with her night attire uncomfortably wet.

(c) *Severe Flushing* (rare).—A severe disability causing insomnia, listlessness, and fatigue (20 cases from b and c were already under stilboestrol therapy in this series).

The results after radium were: severe flushings, 5 (4%); moderately severe flushings, 53 (45%); mild flushings, 51 (44%); and flushings absent, 9 (7%).

The incidence of serious and persistent attacks of flushing after irradiation is three times the normal, or approximately the same as that following surgical castration (Table I).

TABLE I.—Comparison of Menopausal Flushing*

	Pre-menopausal	Post-menopausal	Radium	X rays	Castration	Hyst. Only
No. of cases	74	78	118	17	43	67
Incidence of severe or moderately severe flushing	7 (9%)	13 (17%)	58 (49%)	10 (59%)	20 (46%)	1 (1.5%)

* Comparative figures from previous report (McLaren, 1941).

On the other hand, simple hysterectomy with conservation of ovarian tissue is not followed by the immediate onset of these symptoms. Moreover, the reservation of radium for patients nearer to 50 than 40 years of age does little to alter the incidence of severe flushing (McLaren, 1941).

Spontaneous Cure of Flushing.—It is commonly held that the passing of a few months will cure flushing, and that a little encouragement is all that is required from the doctor. With this in mind we carefully investigated 71 patients who had completed the radium menopause for periods up to four years (average two years), to find that a spontaneous cure had resulted in only 13 cases, while four appeared to be more seriously affected with the passage of time. The remaining 54 cases (76%), however, continued to have flushing of unabated severity, so that "radium" flushes are by no means transient.

* A postgraduate lecture delivered at the Royal College of Obstetricians and Gynaecologists on November 18, 1949.

Sex Function After Radium.—Before any pelvic operation or treatment by radium or x rays there arises in the patient's mind the question, "Shall I be able to continue my normal married life?" At the time of writing no adequate controls are available—that is, it is not known how many women become sexually anaesthetic after the normal menopause. It is considered; nevertheless, that the sudden loss of libido and the onset of sexual dysfunction after radium should be recorded.

Method of Study

The difficulties in obtaining accurate information and the degree of selection of cases were as follows: (1) Before radium treatment uterine bleeding had often caused both physical and mental disturbances, so that sometimes sexual activity had been minimal for months. (2) When patients could not be questioned about sex function—for example, embarrassed patients, unmarried women, widows, or women with unfit husbands. (3) When the patient was obviously telling us what she thought might be expected of her—for example, when a woman, alleging normal sex life, was found to have a painful lesion of the vulva or vagina. (4) Lastly, in all cases the sexual performance of the male partner could only be guessed at from questioning the patient.

I interviewed all the patients in privacy, and after a general talk about weight, flushings, amenorrhoea, etc., the subject of sexual function was tactfully opened. After ascertaining that the husband was healthy, I explained that we were anxious to know if their married life had been improved or in any way altered since the cure of menorrhagia. In various forms the following questions were put:

1. "Before treatment, how frequently did intercourse take place—twice weekly or oftener?" Very often the question "after radium" was answered by a shrug, "Oh, I quite lost interest," or, "It became quite hopeless."

2. The orgasm was also discussed in the simplest terms. "Do you get complete satisfaction, just like your husband?" "Do you get satisfaction always, or once every two or three attempts?"

Very occasionally the male partner was accused of being precipitate or ineffective, but more often the patient herself admitted the sudden onset of sexual anaesthesia, sometimes aggravated by loss of secretion at the vulva.

Material

Half the patients were from Aberdeen and district and half from Birmingham and the Midlands. Information was available from a total of 236 cases. The variable ages of the patients were:

Group A: Aberdeen (116 Cases)

Age	No.	Age	No.	Age	No.	Age	No.	Age	No.
27	1	40	3	45	8	50	4	55	3
34	1	41	4	46	10	51	12	56	1
36	1	42	9	47	12	52	3	57	1
37	2	43	7	48	4	53	6	58	2
38	4	44	6	49	9	54	2	61	1

Group B: Birmingham (120 Cases)

Age	No.	Age	No.	Age	No.	Age	No.	Age	No.
33	1	38	1	43	9	48	12	53	9
34	1	39	4	44	5	49	6	54	5
35	1	40	3	45	5	50	4	55	2
36	2	41	9	46	9	51	5	56	2
37	2	42	7	47	10	52	5	58	1

The following is an outline of the degree of selection. **Sex Urge**:—Computed from desire for intercourse or libido plus frequency of intercourse; 76 patients could provide no information (unmarried, widows, those with unfit husbands). The evidence was discarded as unreliable in 17 and accepted in 143. **Orgasm**:—No information, 79; evidence discarded, 31; reliable information available, 126.

Effect of Radium on Sex Urge

Before Radium.—Good, 11 (7%); moderate, 66 (46%); slight, 43 (30%); absent, 23 (16%)—a total of 143 cases. In other words, 66 (46%) of our cases either lacked or had only slight libido before treatment with radium. The remaining 77 cases (54%), however, had normal sexual desire and would therefore have reason to complain if they found themselves anaesthetic or completely disinterested as a result of radium treatment.

After Radium.—(1) 11 patients with "good" sex urge:—Unchanged, 7 (64%); depressed to "slight," 1 (9%); complete loss of libido, 3 (27%). (2) 66 patients with moderate sex urge:—Maintained, 15 (23%); depressed to "slight," 9 (13.5%); complete loss of sex urge, 42 (63.5%). (3) 43 patients with "slight" sex urge:—Improved to "moderate," 2 (4.5%); unchanged, 14 (32.5%); complete loss of sex urge, 27 (63%). (4) 23 patients without sex urge:—Unchanged, 23.

To summarize: sex urge already depressed or lost in about 50% of cases suffered further as a result of radium castration; for of 77 patients estimated to have normal sex urge 55 (71%) suffered a marked diminution or found themselves entirely without libido.

Effect of Radium on the Orgasm

Before Radium.—Orgasm usually or almost always, 65 (51.6%); orgasm occasionally, 30 (23.8%); orgasm never achieved, 31 (24.6%)—a total of 126 cases. In other words, 61 (48.4%) were unable to achieve the orgasm or did so only occasionally, while 65 (51.6%) normally achieved the orgasm, and would therefore have reason to complain if this faculty were lost as a result of radium castration.

After Radium.—(1) 65 patients who normally achieved the orgasm:—No effect (orgasm maintained), 28 (43%); depressed (occasional orgasm), 14 (21.5%); absent, 20 (30.7%); doubtful, 3 (4.6%). (2) 30 patients who occasionally achieved the orgasm:—No effect, 11 (36.7%); complete loss of orgasm, 19 (63.3%). (3) No orgasm before or after radium, 31 (24.6%).

As will be seen, the orgasm, already infrequent or absent in 61 cases (48.4%), was further affected by radium, so that 34 patients (52%) who normally achieved the orgasm found this no longer possible.

Dyspareunia after Radium.—Although the commonest symptoms after the use of radium were sudden loss of libido and a loss of normal genital sensation, dyspareunia was also present in at least 10% of cases. Occasionally patients noticed that lack of normal vulvar secretion at coitus aggravated the condition.

Premature Ageing of the Genital Tract after Radium

The Vulva and Introitus.—Vulvitis secondary to vaginitis was observed in 2 out of 82 cases, but the introitus appeared abnormal in 7 out of 72 cases—in fact, in 5 patients pain prevented the passage of a small speculum.

Atrophic Vaginal Changes.—Total number of Cusco examinations, 68; bleeding mucosal spots, 11 (16%). Clinically, we labelled these spots "senile vaginitis."

TABLE II.—Abnormal Introitus

Case No.	Age	Condition of the Introitus
53	48	Red and inflamed but not painful
184	36	Painless telangiectasis
185	48	Involved in senile vaginitis
188	52	Perineo-vaginal junction split and bled easily
187	39	Tender inflamed introitus
263	58	Tender; periurethral oedema present
103	53	Tender inflamed introitus

although "pre-vaginitis" would perhaps be a more accurate term; for in our experience it requires the irritation of, say, a pessary before purulent vaginitis develops. In Table III

TABLE III.—*Vaginal Spotting*

	Normal Menopause		Post Radium		Castrate		Simple Hysterectomy	
	Average age, 63		Average age, 46		Average age, 45		Average age, 40	
	Red Spotting		Red Spotting					
	Macro.	Biopsy	Macro.	Biopsy	Macro.	Biopsy	Macro.	Biopsy
No. of cases	57	23	68	88	36	27	75	34
Atrophic or senile ..	15 (26%)	8 (35%)	11 (16%)	13 (14%)	4 (11%)	7 (26%)	0 (0%)	1 (3%)

comparative figures from a previous report (McLaren, 1941) show clearly that surgical castration, like radium, may produce senile mucosal spotting, whereas functional ovarian tissue prevents it.

The Cervix.—The following is a summary of the effect of radium on the cervix: (a) atrophy down to the merest rudiment, 27 of 100 cases (27%); (b) red spotting on the portio, 9 of 75 cases (12%); (c) flat erosions without mucopus, 10 of 131 cases (13%); (d) cervical mucus, 56 cases: absent or traces of mucus, 33 (59%); small amount of mucus, 23 (41%). A great variety of bizarre-shaped cells appear in the endocervical canal after irradiation, while radium-vacuolation was occasionally observed in the cytoplasm even six months after treatment. The commonest cells were the polymorph and the endocervical cell, 7 to 10 μ in diameter and possessing a relatively large nucleus. Large "fibre" cells 120 to 180 μ in length with rod-shaped nuclei and small squamæ were also seen. Mucus in crenated or web-like form replaced the clear mucus of the sex-mature cervix. On one occasion, however, a small clear piece of mucus was found to contain abundant spermatozoa.

The Urethra.—In a previous report on patients over 60 we noted that in the normal menopausal urethra the external urethral orifice might occasionally show a tongue-like projection of mucosa. These protuberant areas were painless and did not bleed; they were considered to be physiological and not true caruncles. No such appearances were seen in this series. The recent work of H. G. Hanley (1944-5) on menopausal trigonitis and urethritis led us to search for this condition, but only two cases with frequency, sterile urine, and typical trigonal lesions have so far been discovered. (Mr. Guy Baines undertook the cystoscopic examinations.) Urethral smears were taken from 47 smears and compared with the normal. Only three smears could be labelled senile or immature with deep or undifferentiated small cells. The remainder were within normal limits—namely, clumps of intermediate cells (40 μ in diameter), small squamæ, globular cells with long nuclei, leucocytes, free nuclei, and so on. Evidence of urethral irradiation was occasionally seen in cytoplasmic and nuclear vacuolation up to six months after treatment.

Vaginal Smears Reflecting Ovarian Activity

Vaginal smears can forecast the actual mucosal histology (1) with adult or mature cells (= adult differentiated epithelium), and (2) with very small or immature cells (= senile undifferentiated epithelium). Most menopausal smears were neither adult nor completely senile. Many smears had a large number of intermediate cells, and though they cannot always be correlated with the histology of the mucosa they do portray a degree of senility or lack of maturity. With these limitations of the vaginal smear in

mind, 67 were classified as follows: grossly senile (grade I), 2; moderately senile (mixed or grade II), 44; menopausal clumping (grade III M), 19; and adult, as in sex-mature women (grade III), 2.

Seventy per cent. of the smears therefore had varying numbers of intermediate or senile cells. The 19 smears showing menopausal clumping resembled mid-pregnancy smears, and, indeed, in one case (after 17.5 g. of vitamin E, however) the pregnancy-like or "luteal" smear was found at laparotomy to correspond to the presence of a post-menopausal luteal cyst of the ovary (McLaren, 1949). These menopausal "pregnancy-like" smears appeared to have smaller flat cells lying superficial to deeper and larger cells. It is not suggested, however, that the hormone levels of pregnancy and the menopause are similar, although the resulting vaginal smears may be alike.

The presence of deeper mucosal cells in 70% of the smears probably results from a deficiency of ovarian hormones, and this is supported by the fact that flat squamæ replace less mature cells after small doses of stilboestrol. The other possibility is that senile (menopausal) cells result from an excessive level of androgens or a new and increased response to a hormone of this type which is capable of depressing the maturation of the vaginal mucosa. Whatever the exact hormone pattern which produces senility or maturity in cell smears, there is no relation between the cytology and the severity of symptoms; so that patients with no flushings, for instance, produce senile smears and, vice versa, patients suffering intensely from flushing may have a relatively adult cell smear.

Miscellaneous Findings

Ignorance of the diagnosis and the aim of treatment was striking both in this series and in the Aberdeen group—for example, eight patients still practised contraception, while several admitted that they thought they had had cancer. One patient had amenorrhoea and a large abdomen, and was lactating freely. She was busily occupied in knitting baby-clothes for her pseudopregnancy.

Discussion

From the foregoing, the radium menopause is apparently free from any severe delayed effects, but flushings, sexual anaesthesia, and mild involutional changes in the genital tract may be important if not severe disabilities. Most of these ill effects can be improved by the use of stilboestrol. Indeed, 19 of our patients were already under stilboestrol treatment for flushings by their own doctors. However, 40 patients were suffering the discomfort of flushings with loss of sleep, etc., apparently content with the assurance that the effects of the "change" are inevitable and would soon cease.

Flushing and Sweating

Fifty per cent. of normal women approaching the menopause experience occasional flushes or sensations of heat, but in only one case in ten are they of serious type. The figure rises to 17% after the menopause and to 50% after radium or castration (McLaren, 1941). This figure is in agreement with that of Schmitz and Towne (1947), who recorded 48% with "serious menopausal manifestations" in 412 cases treated by x rays or radium.

To the severity of "induced" flushes must be added their suddenness of onset. In contrast to this, the normal woman is usually given time to become used to flushes, which may or may not slowly increase in frequency and intensity.

The similarity of the incidence of flushing after radium and castration raises the question—so far unanswered—

of the aetiology of flushing. Does radium destroy the ovary, or is its chief effect on the endometrium, finally preventing it from reacting to hormone stimulation? There seems as yet no clear answer, though probably both endometrial and ovarian irradiation are important in producing amenorrhoea. Ovarian damage and reduced secretion of follicular and luteal hormones (as reflected, for example, in the vaginal smears) may permit overaction of the anterior pituitary, but why this leads to uncontrolled flushing and sweating is not clear.

Loss of Libido

Do women normally become disinterested in sex matters at the menopause? I was somewhat discouraged in several attempts to find a suitable group of (gynaecologically) normal patients—for example, in the surgical wards. So far no controls are available to compare with patients who have been irradiated. Nevertheless, it seems an important finding that libido practically disappeared in well over half the patients under review. The cause of sexual anaesthesia would appear to be more than a temporary effect of irradiation on the sensory-nerve endings in the genital tract, for that might be expected to resolve in time. Ovarian sclerosis with loss of ovarian hormone is another possibility, but it is well known that some castrated women may continue to have a normal and satisfactory married life. The mere fact that the patient has amenorrhoea and knows that she can no longer bear children may, however, be the main factor in disturbing normal sex function.

There seems little doubt, therefore, that radium treatment quickly leads to sexual anaesthesia in 50% of women with normal sexual feelings. It may be that a similar group of patients passing through the normal menopause would likewise find themselves without interest in sex matters, but that does not detract from the fact that radium has caused this *prematurely*.

If, when adequate controls are available, it is found that the normal menopause also leads to sexual anaesthesia in a high proportion of cases, that will provide no support for the induction of the menopause except when it is obvious that no other method of therapy is effective. The development of sexual anaesthesia is a serious matter whether inevitable in the normal menopause or not, and to avoid it our future efforts must obviously aim at a method of controlling haemorrhage short of induction of the menopause.

Premature Involution of the Genital Tract

The occurrence of two cases of vulvitis, five with painful lesions of the introitus, and 11 with red "blood spots" on the vagina perhaps does not portray a picture of serious clinical lesions. But add the fact that dyspareunia was present in at least 10%, and that many of the patients suffering from newly developed sexual dysfunction no longer had Bartholin's secretion at coitus, and it will be obvious that radium does more than simply produce therapeutic amenorrhoea.

Mucosal Spotting.—The passing of a Cusco speculum with distension of the vagina seldom causes punctate areas of bleeding in the vaginal mucosa before the menopause, although in a previous study in normal post-menopausal women in the sixth and seventh decades the condition was found to be quite common—namely, 15 out of 58 (26%) (average age 63). Moreover, in younger women, after surgical castration, similar vaginal spots were found in 11% of cases (McLaren, 1941). It is not possible to say how many years must elapse before these atrophic changes become common in the normal woman, but the appearance

of "senile spots" in 16% of cases after radium treatment (aged about 45) is unusual and almost certainly it is a consequence of irradiation. Since small doses of stilboestrol cure the condition it seems likely that lack of ovarian hormones is in fact the cause, and this is borne out in Table III, which clearly shows that conservation of ovarian tissue at hysterectomy prevents, or at least postpones, involutional changes in the vagina. The histological appearance of these "blood spots" is typical, whether on the portio or in the vagina—namely, the superficial epithelium is missing, so that only a few layers of small epithelial cells separate the lumen of the vagina from the submucosa. At the site of the epithelial defect there is a clustering of round cells, but no marked dilatation of blood vessels such as one sees in true senile vaginitis.

The red spotting of the vagina therefore seems to represent a deficiency of ovarian hormones and constitutes a potential rather than an actual disability—that is, it may be only after insertion of a pessary, or after coitus, that a true senile (purulent) vaginitis develops.

The Cervix.—In cases of persistent uterine bleeding in which either radium or surgery would suffice, after curettage has excluded cancer of the uterus, the scales are often tipped in favour of surgery by the presence of a hypertrophic eroded cervix from which excessive amounts of mucopus exude. The choice of surgery implies that the cervical condition will not be cured by radium, but, in fact, in our observations we have never seen a cervix after the radium menopause which produced excessive quantities of mucopurulent discharge. On the contrary, after radium treatment the cervix secretes little or no mucus and becomes less bulky, even atrophic. It is important, therefore, in assessing a clinical case to recognize that the radium menopause will cure what seems to be an unhealthy cervix and relieve symptoms arising from mucopurulent cervical discharge.

Comment

Apart from emphasizing the effects of castration by radium or any other method, our investigations do not answer the difficult clinical problem of selecting the safest and best method of treating a specific case of simple menorrhagia at or near the climacteric. After diagnostic curettage it is often good practice to delay a decision on final treatment, sending the patient to a convalescent home, where rest, fresh air, iron therapy, and so on may continue to improve her general condition.

Especially in metropathia, it is not uncommon for temporary, or even permanent, recovery to follow these simple measures. Very often, however, even after attempts at control with hormone therapy, a decision has to be given on treatment aimed at producing amenorrhoea. The definite morbidity and mortality of hysterectomy *versus* the safety and simplicity of x rays or radium is a lengthy subject which will not be discussed here. If, however, irradiation is chosen (and it rightly finds favour in the Birmingham school for certain cases), it is clear that several years of follow-up should be planned. The need for this is exemplified by the fact that, although 19 patients had reported menopausal flushings and were under hormone treatment by their own practitioners, 40 were not being treated, to say nothing of those who obviously required help in restoring their normal married life.

It seems logical and practical that follow-up examinations should fall to the gynaecologist who induced the menopause rather than to the patient's private doctor, who may or may not have retained the report on the pelvic pathology. If patients are seen at three-monthly or four-monthly

intervals for three years, or at least given the opportunity of visiting the clinic if they have any symptoms, severe flushing and minor genital lesions would be diagnosed and a correct dosage of stilboestrol established. By these simple measures most of the criticism levelled at radium could be met and further support given to it as a safe and effective agent in dealing with intractable bleeding at the menopause.

Summary

Severe or moderately severe flushing may persist for months or years in 50% of cases after the radium menopause (three times the normal incidence).

Only 50% of patients had interest in sex matters before treatment. Of the remainder every other case quickly became sexually anaesthetic after radium treatment. (No "controls" are available.)

Premature senility of the lower genital tract may follow soon after radium—for example, 5 out of 72 had a tender inflamed introitus, and 11 out of 68 had "pre-vaginitis" (red spots).

Responsibility for detection and treatment of the effects of radium rests with the gynaecologist rather than with the practitioner.

This report has been read and criticized by Professor H. N. Lloyd, Mrs. B. M. Willmott-Dobbie, Professor Dugald Baird, Dr. John Hewitt, and Dr. A. C. Crooke. Although unable to answer all the points they raised, it is a pleasure to acknowledge their help and useful suggestions. My thanks are also due to Sister M. Scotwell and to our technician, Miss M. E. Attwood, for their assistance in preparing this report.

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OBSERVATIONS ON THE TREATMENT OF THYROTOXICOSIS

BY

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There is much diversity of opinion regarding the treatment of thyrotoxicosis. Discussion still centres mainly on the relative merits of thyroidectomy and thiouracil treatment. Neither of these methods can, however, be regarded as wholly satisfactory, and no one would claim invariable success with either. An appreciable proportion of patients are found to relapse after either form of treatment; neither is completely devoid of risk, and there is the possibility, particularly after surgical treatment, of such sequelae as malignant exophthalmos or myxoedema. It is of course recognized that complete remission of thyrotoxic symptoms is obtained in a large number of cases treated either surgically or medically.

Astwood (1948), reviewing 400 cases treated with thiouracil, found that 85% of cases obtained satisfactory remission. Carrick Robertson (1948) noted improvement with the use of this drug in 62% of patients under the age of 21, but only in 43% of a series of 116 cases of all ages, while he claimed almost universally successful results with thyroidectomy. On the other hand, Goldman, cited by Astwood, obtained lasting relief in only 41.8% of cases treated surgically, and Vander-Laan and Swenson (1947) considered the results of thyroidectomy wholly satisfactory in only two-thirds of their cases.

Despite the satisfactory results not infrequently obtained in the treatment of thyrotoxicosis, it is apparent that the current methods are not always successful and that relapses are not uncommon. The purpose of this paper is to inquire into the circumstances which might determine this variability in response to therapy. The investigation is based on the examination of 265 patients referred to me on account of suspected thyrotoxicosis.

Diagnosis of Thyrotoxicosis

While the frank thyrotoxicosis of typical Graves's disease is easy to detect, many cases present difficulty in diagnosis. The recent method of studying excretion of radioactive iodine in the urine has emphasized rather than eliminated this difficulty, as it has shown that there are many "border-

TABLE I.—Analysis of 265 Cases Referred to Clinic Suspected to be Suffering from Thyrotoxicosis

Group	Female	Male	Total
A. Thyrotoxic	116	28	144
B. Goitrous but not thyrotoxic	91	2	93
C. Neurosis—no goitre or evidence of thyrotoxicosis	22	6	28
	229	36	265

FIG. 1.—Percentage of patients in each age group.

line" or doubtful cases. In any case of suspected thyrotoxicosis, nervousness is a feature. The combination of nervousness and thyroid enlargement may be wrongly taken to indicate thyrotoxicosis, as the thyroid may not be overactive although large, while, particularly in men, marked hyperthyroidism or thyrotoxicosis may exist with but slight increase in the size of the gland. Exophthalmos may occur without thyrotoxicosis and may be aggravated by thyroidectomy. Tachycardia is commonly found in nervous patients, whether thyrotoxic or not. Auricular fibrillation in a heart otherwise apparently normal is probably most commonly the result of thyrotoxicosis, but the latter condition may be quiescent although the cardiac irregularity persists. The B.M.R. is certainly raised in thyrotoxicosis, but it may be extremely difficult to obtain a truly basal estimation in a tense, nervous patient, and, in such, high figures may be recorded even in the absence of hyperthyroidism. While the blood cholesterol is commonly below normal its value is too variable to be of much diagnostic help.

Recognizing these difficulties, it is not surprising that in by no means all the cases in the present series could the diagnosis of thyrotoxicosis be accepted. Of the 265 cases,