become pregnant: the semen was always fertile—and there is no question of non-motile sperms becoming motile, nor of the suggestion that non-motile sperms could cause pregnancy.

One patient in the authors' series had a serious staphylococcal abscess and sinus "which continued to discharge until the silk suture was extruded from the wound." To use black silk in order to "permit subsequent identification" shows a lack of confidence in the operator's method. (I gave up using silk to ligate the vas after seeing several stitch abscesses with silk protruding from the wound.) In my series of 240 vasectomies, using catgut for ligating the vasae, I have never had a stitch abscess or skin infection.

Finally, may I venture an explanation for the large number of patients who were still producing sperms 6-18 months after vasectomy. Often the vas is long, tortuous, and very mobile, and it is quite easy to ligate and remove a section of the same vas twice. To avoid this it is essential to open the scrotum well away from the midline and to bear this possibility in mind.—I am, etc.,

J. SLOME

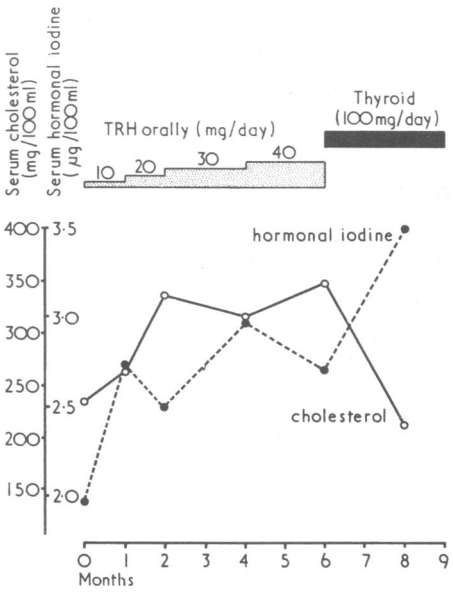
London W.1

Effect of Thyrotrophin-releasing Hormone on Serum Cholesterol

SIR,—In the past 1½ years we have treated eight patients with oral doses of thyrotrophin-releasing hormone (TRH) 10-40 mg/day for periods of 2-15 months. The patients had either mild hypothalamic hypothyroidism or an intractable depressive syndrome; one of the latter patients has been briefly reported on before.[1] Serum hormonal iodine[2] and cholesterol levels were determined serially.

In five of the eight patients a significant and generally marked increase in serum cholesterol concentration was observed during TRH treatment (see table). The effect did not appear to be dose-dependent. All patients were clinically euthyroid at the time the cholesterol values were increased and their hormonal iodine values were higher than before the treatment was started. In one of these five patients (case 6) thyroid tablets were substituted for the TRH therapy after six months. Within two months the serum cholesterol concentration had fallen to normal (see fig.).

It has been known for a long time that serum cholesterol values are normal in many patients with secondary (that is, suprathyroidal) hypothyroidism.[3] This has commonly been attributed to concomitant (often subclinical) hypoadrenocorticism. Reports on serum cholesterol in patients with *isolated* deficiency of thyrotrophin (TSH)—or TRH—are too few for the role of adrenocortical function in this respect to be assessed. In



the light of the present observations it seems likely that at least part of the increase in serum cholesterol seen in primary hypothyroidism is mediated by the chronic hypersecretion of TSH or possibly TRH occurring in this disorder.

Whether the observed increase in serum cholesterol is a direct effect of TRH or is secondary to chronic stimulation of the secretion of TSH, or possibly prolactin, is as yet unknown. The possible influence of TRH on other serum lipids is now being studied.—We are, etc.,

MARY J. E. VAN DER VIS-MELSEN
JAN D. WIENER

Department of Medicine,
Academisch Ziekenhuis der Vrije Universiteit,
Amsterdam, Holland

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Breast Cancer Regression under Oestrogen Therapy

SIR,—In a recent article for debate Dr. B. A. Stoll (25 August, p. 446) puts forward a hypothesis concerning breast cancer regression and oestrogen therapy, the hypothesis being required since oestrogens had been shown to stimulate prolactin release. He suggests that inhibition or stimulation of tumour growth by oestrogens may depend on "the absolute and relative concentrations of prolactin and oestrogen activity available at the site" and that a theory of multiple clones in tumours cannot explain some observations made during treatment. Further he concludes that a tumour requiring both prolactin and oestrogen for maintenance of growth would be inhibited by *both* endocrine ablation *and* high-dosage oestrogen therapy. We would like to raise the following points, in debate.

(1) Evidence cited to support a stimulation of prolactin release by oestrogens was based on an experiment in rats[1] and unpublished findings in man. The scientific content of the latter cannot be assessed, while high doses of oestradiol in ovariectomized rats had a smaller effect on serum prolactin concentration than low doses. It is not always simple to equate results from animal experiments with expected results in man, and there are qualitative species differences in hormonal control of prolactin release and breast tumour induction by exogenous hormones.[2]

(2) Oestrogens at a dose similar to that described by Dr. Stoll are used to prevent or suppress lactation, an observation difficult to reconcile with a further increase in plasma prolactin concentration, especially since serum prolactin is increased in the third trimester by a factor of 30 over non-pregnant values[3] and remains elevated during early lactation.

(3) The incidence of abnormal mitoses detectable by light microscopy is increased in all malignancy.[4] It seems highly likely therefore that daughter cells with differing chromosome material are constantly produced, and that many clones are likely to be present in any particular tumour. While some daughter cells would perhaps be less fitted for survival, some might be more capable of surviving various environmental conditions.[5] This is supported by the observation that different sites and metastases of individual tumours in the same patient show marked variation in oestrogen-binding receptors (O.B.R.).[6 7] Further, one patient with an O.B.R.-containing tumour responded to endocrine manipulation, but after a subsequent relapse did not respond and O.B.R. were then absent.[8] Some animal tumours contain both cancer cells and cancer-host hybrid cells.[9]

(4) The alternating response in Dr. Stoll's first case can, in contrast to his hypothesis, be explained by the clone phenomenon. This eventual escape of tumour response from oestrogen therapy, coupled with inhibition of growth on oestrogen withdrawal, may be an example of selection of a clone requiring oestrogens for growth. It has been suggested that androgen-dependent breast cancer might be induced by prior androgen therapy stimulating a specific clone,[10] though this has been questioned.[11]

(5) The statement that a tumour might be inhibited by both an absence and a gross excess of oestrogen is difficult to understand. However, even if true it would again be evidence in favour of at least two clones, one sensitive to oestrogen lack and the other sensitive to oestrogen excess.

(6) The role of prolactin in human breast cancer requires some comment. Plasma prolactin concentration is reported to be the same in women with untreated breast cancer as in controls.[12] Levodopa, which reduces plasma prolactin, has relieved pain in some patients with extensive breast carcinoma,[13] but this drug induces extensive endocrine effects at many sites. Dr. Stoll induced one remission with levodopa com-

Case	Sex	Age (years)	Dose of TRH (mg/day)	Serum Cholesterol (mg/100 ml; normal: 150-250 mg/100 ml)							
				before	1 month	2 months	3 months	4 months	6-7 months	9-10 months	11-15 months
1	F	52	10	244	279	290	298			325	437
2	F	42	10–20	186	201	197	201				162
3	M	38	10–40	325	360		402	321	468	410	
4	F	54	20	205	213	263					
5	F	23	30	174	174	283	259				
6	F	21	10–40	236	263	337		317	348		
7	F	19	40	178	162	162	162				
8	M	33	40	194	197	190	197				

bined with oestrogen.[14] Phenothiazines have been shown to increase plasma prolactin[15] and might possibly be associated with an increased incidence of breast cancer.[16] Male patients with gynaecomastia, except when associated with drugs like phenothiazines, do not have raised prolactin levels,[13] so that this hormone may not be necessary for breast growth (normal or abnormal) in humans.

In summary, we agree that breast cancer response to hormones is a most complex subject. However, we suggest that the theory of different clones within one tumour or its metastases adequately explains variable responses to endocrine manipulation.—We are, etc.,

P. GARCIA-WEBB
M. H. BRIGGS

Alfred Hospital,
Prahran, Victoria,
Australia

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Levodopa and Growth Hormone Secretion

SIR,—In your leading article on "Glucagon and Growth Hormone" (27 January, p. 188) you state that glucagon stimulation is an effective test of growth hormone release but, since it is less reliable and takes longer to perform than the insulin test, it should be regarded only as "a good second-line test." Though Drs. C. T. Sawin and M. L. Mitchell (1 September, p. 499) have pointed out that the reliability of the glucagon provocative test can be improved by pretreatment with propranolol,[1] we should like to draw attention to another reliable test of growth hormone release, using levodopa as the stimulant, which has recently been investigated by several authors, including ourselves.[2-4] The preliminary results of our study of the effect of levodopa on growth hormone release in elderly normal subjects and in elderly subjects with cerebrovascular hemiplegia are reported briefly here.

Plasma growth hormone levels before and after a single oral dose of levodopa (500 mg) were measured by a double antibody radioimmunoassay technique in seven clinically normal elderly subjects aged 64-83 (average 77·0) years and in seven elderly patients aged 66-76 (average 72·4) years with arteriosclerotic hemiplegia of at least three months' duration. Mild side effects of levodopa (nausea) were noted in only four of the 14 subjects. Significant peak levels of growth hormone were found, usually between 60 and 90 minutes after levodopa administration, in 11 of the 14 subjects investigated. There was no significant difference in response between the hemiplegic patients (mean peak plasma growth hormone level (± S.D.) 21·7 ± 6·41 ng/ml) and the control group (26·14 ± 5·43 ng/ml). Nor was any significant difference noted between the responses of these two groups of subjects and those of normal adults previously studied.[4]

These results confirm that levodopa stimulation should be regarded as a reliable test of growth hormone release in patients of all ages. Moreover, the test is short in duration, does not require any intravenous infusion or injection, and does not involve any risk of hypoglycaemia.—We are, etc.,

C. F. COLUCCI
S. Maria della Pace Hospital
B. D'ALESSANDRO
A. BELLASTELLA
R. GASBARRO
Institute of Medical Semeiotics and Constitutional Medicine,
University of Naples,
Naples, Italy

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Serum Thyrotrophin and Lipid Levels in Summer and Winter

SIR,—Studies in laboratory animals have shown a significant increase in the serum thyrotrophin (TSH) level and thyroid function on exposure to cold. Fisher and Odell[1] found a small rise in plasma TSH in 12 men exposed to seven days of arctic temperature. Ingbar *et al.*[2] have reported that serum protein-bound iodine (PBI) levels are reduced during prolonged cold exposure. Such a reduction in the PBI level might be an explanation of the rise in TSH level observed during exposure to cold.

We have examined the possibility that variations in outdoor temperature may influence the TSH level in persons living and working indoors in houses with central heating. In Sweden the difference in mean outdoor temperature between summer and winter can reach 20-30°C. A seasonal variation in the serum cholesterol level has been noted, with slightly higher levels during winter than in summer.[3,4] Estimations of serum cholesterol and serum triglyceride were therefore included in the study.

The serum TSH values of healthy 50-60 year-old men were measured. Blood samples were taken from 30 men in August 1971 and from 30 men in January 1972. The mean temperature in August was +15·3°C and in January −5·5°C. There was thus a difference of 20·8°C. The sera from both groups were separated, frozen, and stored in liquid nitrogen. All the samples were analysed at one session. The immunoreactive TSH in 0·1 ml of serum was assayed by a radioimmunosorbent technique[5] using ^{125}I-labelled human pituitary TSH (National Pituitary Agency) and anti-TSH coupled to cyanogen bromide-activated Sephadex. The standard (Medical Research Council HTSH research standard A) was dissolved in serum with undetectable or low levels of TSH. The limit of sensitivity was 0·5 μU/ml. The cholesterol and triglycerides were assayed in an isopropanol extract of serum by using a Technicon dual-channel system (N-24A and N-70).

The mean values for serum TSH, cholesterol, and triglyceride levels in August were not significantly different from those in January (see table). We conclude that neither the TSH level nor the levels of cholesterol and triglyceride in serum in healthy men living and working indoors in a country such as Sweden are influenced by seasonal variations in outdoor temperature.

H. HEDSTRAND
L. WIDE
Departments of Internal Medicine and Clinical Chemistry,
University Hospital,
Uppsala, Sweden

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False Interpretation of Fetal Heart Monitoring

SIR,—Mr. I. L. Craft and his colleagues (29 September, p. 694) have drawn attention to a case in which the maternal rather than the fetal heart rate was recorded by a Hewlett-Packard fetal heart monitor during labour.

The case they describe is one in which, when the fetus was known to have died some time before, a record was obtained on the monitor which proved to be maternal in origin though indistinguishable from a normal fetal heart rate. The explanation for this phenomenon is that once the fetus dies the fetus acts as a conductor for the lower voltage maternal E.C.G. signal which is not cancelled out by the fetal signal. A similar case, with a slower maternal heart rate, has been reported previously.[1] As the authors point out, it is important to be aware that this can happen—on one occasion an unnecessary caesarean section was performed when the fetus had been dead for several hours (personal communication). However, caution must be exercised before making the assumption that the maternal heart rate can

Serum Thyrotrophin and Serum Lipid Levels in Healthy Men in Summer and Winter

	August (30 Subjects)		January (30 Subjects)	
	Geometric Mean	95% Confidence Limits	Geometric Mean	95% Confidence Limits
TSH (μU/ml)	3·57	2·17-5·88	3·27	1·18-9·12
Cholesterol (mg/100 ml)	251	150-419	249	162-384
Triglyceride (mmol/l.)	1·41	0·58-3·40	1·57	0·62-4·00