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 vasa, 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 iodine² 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, supra-thyroidal) 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

¹ Vis-Melsen, M. J. E. van der, and Wiener, J. D., *Lancet*, 1972, 2, 1415.

² Backer, E. T., Postmes, T. J., and Wiener, J. D., *Clinica Chimica Acta*, 1967, 15, 77.

³ VanArsdel, P. P., and Williams, R. H., *American Journal of Medicine*, 1956, 20, 4.

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 rats¹ 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 values³ 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					