Table 2. EFFECT OF AN OVULATION-INHIBITING DOSE OF ICI 46,474 ON CONCENTRATIONS OF PITUITARY LH IN ADULT RATS

Group	Stage of cycle at autopsy	Inhibition of ovulation (%)	Pituitary LH* concentration (95% CL)	Total LH content (μg/gland)	Relative potency (95% CL)
Control	Pro-oestrus	—	2·49 (1·64–3·76)	22·8	100
Control	Oestrus	0	1·00 (0·66–1·51)	11·8	40 (27–59)
46,474†	Oestrus	100	1·70 (1·13–2·55)	18·7	68 (46–101)

CL, Confidence limits.
* In μg equivalents of NIH–LH–S11 per mg wet pituitary (assay by OAAD).
† 0·5 mg/kg, given orally, at 1700 h on the day before pro-oestrus.

with 5 mg/kg of ICI 46,474—that is, ten times the minimum effective dose—it was restored by the same dose (25 μg) of LH (group 5). Furthermore, inhibition of ovulation by the compound (0·5 mg/kg, given orally) could be prevented by concomitant injection of a single subcutaneous dose of oestradiol benzoate (400 μg/rat; group 6). The oestrogen by itself did not affect the rate of ovulation (group 7). When ovulation was blocked by giving the minimum effective dose of the antagonist at 1700 h on the day before pro-oestrus, there was no decrease in pituitary LH between pro-oestrus and oestrus as there was in control rats (Table 2).

These results indicate that ICI 46,474 does not reduce the sensitivity of the ovaries to LH, but that it blocks ovulation by preventing the ovulatory surge of LH from the pituitary—probably by interfering with the discharge, or action, of LRF. The fact that inhibition of ovulation is obtained with an antagonist of oestrogen and can be prevented by simultaneous administration of excess oestrogen suggests that this interference stems from an interruption of oestrogen feedback. It is fully consistent with the hypothesis that the train of events that culminates in ovulation is usually set in motion by positive feedback of ovarian oestrogen.

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Oral Contraceptives and Copper Metabolism

IT has been known for many years[1] that serum copper is increased during the later stages of pregnancy. Exogenous oestrogens produce an increase in both serum copper and the copper-binding globulin ceruloplasmin[2] and it is therefore not surprising that all of the popular oral contraceptives containing potent synthetic oestrogens have been reported to increase serum copper and ceruloplasmin[3–7].

A recent development in oral contraception is the daily administration of a continuous small dose of a synthetic progestogen alone without added oestrogen. Because chronic increases of ceruloplasmin have been suspected as being implicated in the aetiology of certain side-effects of oral contraceptives—notably migraine and chloasma—it seemed worthwhile to investigate the effects of one of these new products on forms of blood copper.

Six normal healthy young women received 0·3 mg daily of norethisterone acetate (a product available under the 'SH–420C' Schering code name). As a control, two other similar healthy young women received the combined 21-day preparation 'Minovlar' (1·0 mg norethisterone acetate + 0·05 mg ethinyl oestradiol). Blood samples were taken by venepuncture after an overnight fast, serum was collected and copper was determined by the diethyldithiocarbamate method[8] and ceruloplasmin by the p-phenylenediamine method[9]. Results of these determinations are shown in Table 1.

Table 1. EFFECTS OF ORAL CONTRACEPTIVES ON SERUM COPPER AND CERULOPLASMIN

Treatment	Duration (months)	Mean values ± S.D. Serum copper (μg/100 ml.)	Serum ceruloplasmin (μg/100 ml.)
None	0	121 ± 15	31 ± 4
'SH–420C'	2 to 4	128 ± 20	33 ± 6
'Minovlar'	3 to 4	235 ± 25	84 ± 5

It is clear that the oestrogen-containing product 'Minovlar' produced a marked increase in serum copper and ceruloplasmin, but that 'SH–420C' had no significant effect. The progestogen component of 'SH–420C', norethisterone acetate, is known to produce in man oestrogenic metabolites[10,11], but the extent of this production and its biological effect are still obscure. Our data indicate that, at the dose level used, no significant amount of oestrogenic substances could have been formed. Indeed, the use of changes in serum ceruloplasmin offers a novel approach to the detection of oestrogenic effects in the human.

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Deferred Action of Juvenile Hormone

WHEN some insect eggs are treated with a synthetic analogue of juvenile hormone the resulting larvae grow normally, but much later their metamorphosis may be inhibited, so that they develop into intermediates or even extra larval instars[1,2]. This has been interpreted by Riddi-