news and views

Ectopic production of HCG subunits

from a Correspondent

THE synthesis of a particular hormone or hormone subunit by tumours derived from a tissue not normally engaged in its production (ectopic production) is now a familiar observation. Endocrine abnormalities in patients can often be traced to the presence of a tumour in non-endocrine tissue. Measurement of raised levels of some hormones circulating in the blood is often used as a biochemical marker of malignancy and to monitor the success of surgery, analogous for example to the use of chorionic gonadotropin assays in women with choriocarcinoma. Human chorionic gonadotropin (choriogonadotropin) (HCG) is synthesised by the trophoblast at a very early stage of pregnancy—within a few days of fertilisation. It provides a critical support to the corpus luteum, which decays in its absence with resulting menstruation, and so is crucial in establishing and maintaining pregnancy. HCG is not normally present in the circulation of non-pregnant females, the only exceptions being patients with choriocarcinoma (Vaitukaitis *et al.*, *Ann. J. Obstet. Gynecol.*, **113**, 751–758; 1972), hydatidiform mole (Crawford, *Brit. Med. J.*, **4**, 715–719; 1972) and patients with cancers that ectopically synthesise the hormone (Braunstein *et al.*, *J. clin. Endocrinol. Metab.*, **35**, 857–862; 1972; Braunstein *et al.*, *Ann. intern. Med.*, **78**, 39–45; 1973). HCG can also be detected in normal testis (Braunstein *et al.*, *New Engl. J. Med.*, **293**, 1339; 1975).

The ectopic production of chorionic gonadotropin in cell lines was first described in Gha-Go cells isolated from a bronchogenic carcinoma (Rabson *et al.*, *J. natn. Cancer Inst.*, **50**, 669–674; 1973; Tashjian *et al.*, *Proc. natn. Acad. Sci. U.S.A.*, **70**, 1419–1422; 1973). Both subunits of HCG were identified. The α subunit of HCG (HCG-α) is nearly identical to the α subunits of thyroid-stimulating hormone (thyrotropin), follicle-stimulating hormone (follitropin) and luteinising hormone (lutropin) whereas the β subunit (HCG-β) is different from the β subunits of the other glycoprotein hormones. The α and β subunits are glycoproteins containing moderate amounts (10–20%) of carbohydrate. Two papers in *Nature* have now shown that these subunits are synthesised and secreted by HeLa cells in culture.

Ghosh and Cox (*Nature*, **259**, 416–417; 1976) used the HeLa 65 and HeLa 71 sublines. They showed by radioimmunoassay with β subunit antiserum that the secretion of small but significant amounts (~ 0.0024 ng per 10^6 cells over 5 d) of immunologically reactive material occurs during culture. It is not clear from the results of Ghosh and Cox whether β subunit production, secretion of the complete hormone or both processes takes place. Furthermore, there is a crucial question of the degree of specificity of antiserum for β subunit, as considered later. Perhaps the most striking result reported by Ghosh and Cox is the greatly increased (1,000-fold or more) secretion of immunologically reactive material when HeLa cells were grown in medium supplemented with 1–5 mM butyrate. The response of the cells to butyrate varied almost linearly up to 20 ng per 10^6 cells over 5 d with butyrate concentration over the range 0–5 mM. This intriguing finding is apparently not specific to HCG production. The levels of activity of placental alkaline phosphatase, which like HCG is produced ectopically by HeLa cells (Elson and Cox, *Biochem. Genet.*, **3**, 549–561; 1969) are also markedly increased by butyrate (Griffin *et al.*, *Arch. Biochem. Biophys.*, **164**, 619–623; 1974). The mechanism of action of butyrate in augmenting synthesis of two glycoproteins is unknown. It may be significant that short chain fatty acids including butyrate, were shown to increase the activity of a sialyl transferase in HeLa cells (Fishman *et al.*, *Biochim. biophys. Acta*, **59**, 292–299; 1974), since sialylation of at least one glycoprotein, thyroglobulin, seems to be obligatory for its secretion (Monaco and Robbins, *J. biol. Chem.*, **248**, 2328–2336; 1973). The substrate specificity of the HeLa cell sialyl transferase(s) responding to butyrate may therefore be of interest in considering its possible role in controlling HCG secretion.

Although the Ghosh and Cox experiments do not distinguish between secretion of β subunit or completed HCG molecules, Lieblich *et al.* (this issue of *Nature*, page 530) show unequivocally that at least some sublines of HeLa secrete relatively massive quantities of α subunit ectopically (about 75 ng per 10^6 cells per day). Unfortunately the HeLa sublines (CCL 2, 2.1 and 2.2) used by Lieblich *et al.*, do not include those studied by Ghosh and Cox. Since the rate of secretion of α subunit varies about 50-fold among the various sublines studied by Lieblich *et al.*, it is possible that HeLa 65 in fact secretes only the β subunit. Alternatively these cells may carry out a balanced synthesis of α and β subunits with secretion of the completed hormone.

The relatively massive secretion of free α subunit by the HeLa sublines studied by Lieblich *et al.*, does however raise the question of what Ghosh and Cox were measuring in their basal system or even in the stimulated cultures. The antiserum used by the latter workers, raised against purified β subunit, is stated to show less than 1% cross reactivity with luteinising hormone indicating even less than this degree of cross reactivity with the common subunit. But such contamination could conceivably account for the small reactivity obtained in the medium of cells grown in the absence of butyrate. It is of course less likely to complicate the measurement of the much larger quantities of immunologically reactive material produced by HeLa 65 cells in butyrate medium although this cannot be entirely ruled out.

The α subunit secreted in such large amounts by HeLa cells is immunologically indistinguishable from α subunit isolated from pregnancy urine. The tumour α subunit is apparently not structurally identical however,

A hundred years ago

ON the 31st ult. a meeting, at which several well-known English biologists were present, took place at the house of Dr. Burdon-Sanderson, at which the advisability of establishing a society or association for the purpose of promoting the progress of physiological research in England, was considered and discussed.

from *Nature*, **13**, April 6, 455; 1876.