72. &-ADRENORECEPTOR BLOCKADE AND PITUITARY HORMONE LEVELS
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The antihypertensive effect of &-adrenoceptor-blocking agents may involve central mechanisms. Chronic propranolol treatment has been shown, for example, to increase total brain dopamine in experimental animals and centrally administered dopamine can lower blood pressure. This effect might be mediated by a direct reduction of sympathetic outflow but dopamine is known also to enhance anterior pituitary hormones, which may themselves affect blood pressure. We therefore measured the effect of the blocking agents on anterior pituitary hormone levels.

A clinical study in hypertensive patients treated with oxprenolol for 1 day or for more than 6 weeks showed no change in the levels of prolactin or growth hormone in single blood samples taken under standard conditions during the day. However, pituitary hormone levels exhibit diurnal variation and fluctuate widely during everyday activities. We have therefore studied the effects of acute and chronic treatment with blocking agents on pituitary hormone levels measured during the hours of nocturnal sleep.

Eight healthy men were given single blind cross-over treatment with a capsule of lactose, acetabutol (200 mg) and propranolol (80 mg) on three occasions at 2 week intervals. Up to 15 blood samples per night were taken from an indwelling venous catheter in order to characterize the time course of these hormone levels throughout the night. The results of the acute study are available and show that a single dose of either acetabutol or propranolol significantly reduced prolactin, follicle-stimulating hormone and testosterone without significantly altering luteinizing hormone, and significantly increased growth hormone and cortisol.

These clinical data provide further evidence that &-adrenoceptor-blocking agents exert a central action in man. Reduced prolactin levels are consistent with a local increase in brain dopamine and could exert an antihypertensive effect via salt and water excretion and reduced arteriolar response to noradrenaline, to which increased growth hormone and cortisol levels could be a secondary response. Clearly &-adrenoceptor blockade disturbs the matrix of cardiovascular homeostatic control mechanisms at many points.

73. PREDICTION OF RELAPSE AFTER DRUG TREATMENT OF GRAVES' DISEASE BY MEASUREMENT OF LATS-PROTECTOR
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It is only by clinical studies that the significance of these assays can be assessed. The tendency for patients with thyrotoxicosis to relapse after drugs offers an opportunity for observing the relationship between Graves' disease and LATS-P levels.

Thirty-eight patients (mean age 38 years, six men and 32 women) were studied after a course of antithyroid drugs (mean duration 16 months). Serum samples for LATS-P assay were withdrawn on stopping antithyroid drugs, at relapse, or, if relapse did not occur, at 1 year. Thyroid function was assessed by plasma thyroxine and tri-iodothyronine. Twenty-five patients relapsed (mean duration to relapse 6-3 months) and there was no difference between these patients and those remaining euthyroid in age, duration of therapy or thyroglobulin and microsomal antibodies at initial diagnosis. Of the 25, 19 had LATS-P activity (mean 12 units) on stopping therapy. In the remaining six patients, however, activity became detectable in only three, and three of the patients who relapsed did not have detectable LATS-P. In 11, LATS-P was not detectable and these remained euthyroid. In the remaining two, activity was detectable on stopping therapy but both had developed permanent hypothyroidism.

These results demonstrate a strong relationship between LATS-P and relapse of thyrotoxicosis after antithyroid drug therapy. The three exceptions in this study, who relapsed without ever having detectable LATS-P, may arise from lack of sensitivity in the assay or to another circulating thyroid stimulator.

74. THYROID HORMONE LEVELS AFTER PROPRANOLOL WITHDRAWAL
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Propranolol withdrawal is characterized by a potentially dangerous rebound increase in adrenergic activity, which is exaggerated in the presence of hyperthyroidism (Ross, Lewis & Henderson, 1979, Lancet, 1, 875). Hyperthyroidism itself results in features suggesting increased adrenergic activity. We have investigated the possibility that changes in thyroid hormone activity could contribute to the propranolol-withdrawal syndrome.

Six euthyroid men and five hyperthyroid women were studied after taking propranolol (160 mg/day) for 4-8 weeks and then for 6 days after single blind substitution by placebo. Venous blood samples were taken daily at 10.00 hours after a standard breakfast and 45 min bed rest. Serum thyroxine (T4) and tri-iodothyronine (T3) were measured by a solid-phase radioimmunoassay and vacant thyroid hormone-binding sites were measured by Thyropac-3 test. Free T4 and T3 indices (FT4, FT3) were calculated as T4 or T3/Thyopac-3 value expressed as a percentage.

Where thyroid hormone levels were normal in euthyroid patients, no change in thyroid hormone levels was seen after stopping propranolol. Hyperthyroid patients showed significant and sustained rises in T4 and FT4 to maximum levels 60 h after stopping propranolol, but no change in T3 or FT3.

Standing heart-rate responses after propranolol withdrawal in these patients have previously shown that adrenergic activity reaches its peak also at 60 h after stopping propranolol. The coincident increase in thyroid hormone activity could therefore contribute to this phenomenon and also possibly reflect the increased adrenergic activity. These findings suggest a special need for caution when stopping propranolol in hyperthyroid patients.

75. EVIDENCE FOR AN IMMUNOSUPPRESSIVE EFFECT OF METHIMAZOLE ON THYROID AUTOANTIBODY PRODUCTION
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Patients with hyperthyroid Graves' disease, treated with carbimazole or its active metabolite, methimazole, show a fall in
thyroid autoantibody production in response to therapy. The autoantibodies are synthesized primarily by lymphocytes situated in the thyroid, and since the drugs are preferentially concentrated by the thyroid we have investigated the possibility that they may be acting directly on thyroid lymphocytes to depress autoantibody production. The techniques used were based on an earlier investigation of the effects of irradiation on autoantibody synthesis (McGregor, McLachlan, Rees Smith & Hall, 1979, Lancet, ii, 442-444).

Peripheral blood lymphocytes from six patients with Hashimoto's thyroiditis were cultured for 14 days in Marbrook flasks in the presence of various concentrations (0-10-4 mol/l) of methimazole (Sigma). The cultures were then assessed for cell viability and synthesis of total immunoglobulin (IgG) and methimazole (Sigma). The cultures were then assessed for cell viability and synthesis of total immunoglobulin (IgG) and specific autoantibody antibodies. All determinations performed in quadruplicate.

Autoantibody synthesis was inhibited by methimazole concentrations as low as 10-4 mol/l. At this concentration mean antibody levels were 79 ± 3% of the control values (n = 6, P < 0-01). Higher concentrations of the drug caused greater inhibition with antibody levels of 66 ± 3% of control at 10-3 mol/l (n = 6, P < 0-001), 51 ± 4% of control at 10-2 mol/l (n = 6, P < 0-001) and 10 ± 2% of control at 10-1 mol/l. Inhibition of autoantibody synthesis was paralleled by a reduction in total IgG production. Cell viability was reduced only by increase in the drug concentration beyond 10-4 mol/l.

These studies indicate that methimazole can directly inhibit autoantibody synthesis. It seems likely therefore that the observed fall in serum autoantibody levels during antithyroid therapy is due to the direct inhibition of autoantibody synthesis by the drug on the autoantibody-producing lymphocytes of the thyroid.

76. MUSCLE PROTEIN BREAKDOWN IN THYROTOXI-COSIS ASSESSED BY URINARY 3-METHYLHISTIDINE EXCRETION

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Urinary excretion of 3-methylhistidine (3MH) is a measure of muscle catabolism. If it is to be used clinically in man those factors which control its excretion need to be defined. In the rat 3MH excretion is influenced by thyroid function (Munro, 1978) (in: Advances in Parenteral Nutrition, p. 117, M.T.P. Press). The purpose of the present study was to investigate the effect of thyrotoxicosis on urinary 3MH excretion in man.

Twenty thyrotoxic patients (three male and 17 female; age range 35-50 years) were studied, while eating their normal diet, at diagnosis and during treatment and the results compared with controls matched for age and sex. Urinary 3MH and creatinine excretion were measured with amino acid analysis and chemical techniques. All subjects had anthropometric measurements to determine fat-free mass (FFM).

In the thyrotoxic group 3MH excretion was 306 ± 31.8 
µmol/day, which fell to 186 ± 15.6 
µmol/day after treatment (P < 0-01) (control group 176 ± 45.1 
µmol/day). When excretion was expressed in terms of fat-free mass (µmol day−1 kg−1 FFM) it also fell significantly with treatment, i.e. 7.5 ± 0.66 to 4.3 ± 0.37 (P < 0-01) (control group 2.8 ± 0.84).

In one patient, who relapsed after treatment, the anthropometric measurements fell and 3MH excretion rose with increasing thyrotoxicity.

3MH/creatinine molar ratio, a measure of fractional degradative rate of myofibrillar protein, fell in the patients from 0.056 ± 0.006 to 0.029 ± 0.02 after treatment. The latter figure agrees with that of Tomas, Ballard & Pope (1979, Clinical Science, 56, 341-346) for subjects on a normal diet.

Assuming 3MH content of muscle to be 4-2 µmol/g of mixed muscle protein (Munro, 1978), muscle protein breakdown in the untreated patient was 70-3 ± 7.86 g/day and 42-2 ± 3.97 g/day when euthyroid (controls 42-0 ± 10-73 g/day).

These results suggest that urinary 3MH excretion can be used to sequentially assess muscle protein breakdown in thyrotoxicosis.

This work was supported by Kabivitrum Ltd.

77. 1,25-DIHYDROXYCHOLECALCIFEROL IN HUMAN VITAMIN D DEFICIENCY

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The changes of circulating 1,25-dihydroxycholecalciferol [1,25-(OH)2D3] concentrations have been followed before and during treatment in patients with osteomalacia due to vitamin D deficiency. Serum 1,25-(OH)2D3 was measured by radioimmunoassay; the normal range is 22-59 pg/ml.

Seven Asian patients were studied for 4-18 months. All had histologically proven osteomalacia, very low serum concentrations of 25-hydroxycholecalciferol (25-OH-D3), hypocalcaemia and secondary hyperparathyroidism. Serial measurements of basal serum 1,25-(OH)2D3 revealed abnormally low concentrations.

Two patients were treated with synthetic 1,25-(OH)2D3, 0-5 pg/day twice daily. On this dose healing of the bone disease occurred without any increase in serum 25-OH-D3 concentrations, which remained very low or undetectable (<0.8 ng/ml) during the course of treatment. The highest serum 1,25-(OH)2D3 concentration observed was 80 pg/ml.

Five patients received therapy with vitamin D3 (3000 units daily) and also showed clinical and biochemical improvement with healing of the osteomalacia. Serum 25-OH-D3 concentrations rose and remained within the normal range throughout the period of observation. This form of treatment resulted in a rapid increase of circulating 1,25-(OH)2D3, which became normal within 24 h. Concentrations continued to rise and reached supranormal values of up to 200 pg/ml, which were sustained for 1-2 months. They then started falling gradually even within the normal range.

These studies indicate that the conversion of 25-OH-D3 into 1,25-(OH)2D3 in man must be regulated in a similar fashion to that previously shown in animals.

78. REGULATION OF PLASMA 1,25-DIHYDROXY-CHOLECALCIFEROL IN PRIMARY HYPERPARA-THYROID PATIENTS

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Important stimuli for production of 1,25-dihydroxycholecalciferol [1,25(OH)2- vitamin D] are hypocalcaemia, hypophosphataemia and increased plasma parathroid hormone (PTH). In patients with primary hyperparathyroidism increased calcium absorption is associated with high plasma concentrations of 1,25(OH)2-vitamin D, although a proportion of patients have low 1,25(OH)2-vitamin D and malabsorption of calcium. A group of patients with primary hyperparathyroidism have been studied before and after parathyroidectomy to establish the relative importance of plasma PTH, calcium and phosphate on the regulation of 1,25(OH)2-vitamin D production.

Eighteen hours after successful parathyroidectomy there was a significant reduction in plasma PTH (P < 0-05), plasma calcium (P < 0-001), plasma ionized calcium (P < 0-001), renal tubular reabsorption of calcium (P < 0-001) and OHPr/Cr ratio (P < 0-05). There was also a significant fall in plasma 1,25(OH)2-vitamin D (P < 0-05). Plasma phosphate was unchanged despite a slight rise in renal tubular reabsorption of phosphate. The fall in plasma PTH and 1,25(OH)2-vitamin D was complete between 18 and 42 h of operation but plasma...