In the fasting state, the p.d. fluctuates between +2 and −2 mV, but the ingestion of food is followed by sustained rises of p.d. to 8–10 mV (lumen negative). Experiments on the isolated vascular-perfused canine duodenum show that the fluctuation of fasting p.d. is associated with spontaneous variations in intraluminal pressure, but sustained elevation of p.d. is induced only by the intraluminal presence of glucose.

These observations suggest that the measurement of transmural p.d. in the human small intestine is now a practicable method for following intestinal function after normal feeding without the use of radio-opaque media.

I am grateful to Mr T. G. Barnett for his expert electronic advice.

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A simple mechanical speed monitor for a bicycle ergometer

BY B. M. WRIGHT. *National Institute for Medical Research, Mill Hill, London N.W. 7*

COMMUNICATIONS

Effects on the isolated neurohypophysis of agents which affect the membrane permeability to calcium

BY J. J. DREIFUSS, J. D. GRAU and J. J. NORDMANN. *Department of Physiology, University of Geneva Medical School, Geneva, Switzerland*

Much evidence supports the idea that calcium plays a key role in the process whereby depolarization of the neurohypophysis leads to an increase in oxytocin and vasopressin secretion. Thus, the presence of calcium in the external medium is required for K-evoked hormone release, and there is evidence that potassium-induced depolarization increases the calcium permeability of the neurosecretory axons (Douglas & Poisner, 1964). We now report that agents which reduce ^{45}Ca uptake in the isolated rat neurohypophysis cause a concomitant reduction of hormone release.

Cobalt, manganese and the drug D600 (Kohlhardt, Bauer, Krause & Fleckenstein, 1972) reduce in a dose-dependent way both the extra

calcium uptake caused by depolarization and the K-evoked hormone release. Calcium uptake and hormone secretion were reduced to about 50% of the control by $MnCl_2$ 10^{-3} M, $CoCl_2$ 10^{-3} M and D600 10^{-5} M (Fig. 1). Lanthanum produces *per se* an increase in hormone release (Matthews, Legros, Grau, Nordmann & Dreifuss, 1973); however, the increase in release evoked by KCl was abolished after preincubation of the neurohypophysis in the presence of $LaCl_3$ 0·5 10^{-3} M.

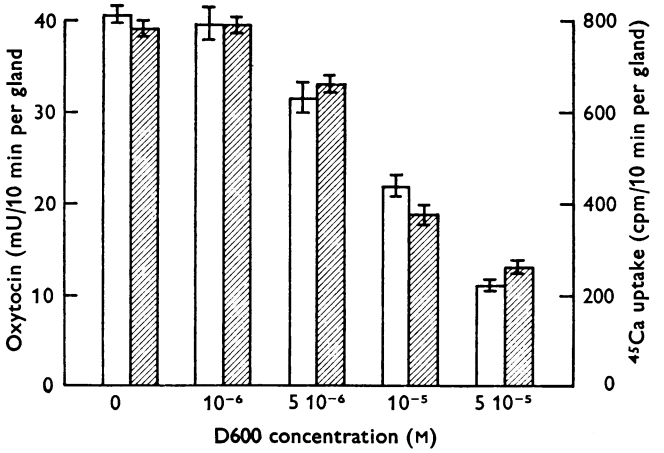

Fig. 1. Effects of various concentrations of D600 on hormone release and ^{45}Ca uptake by isolated rat neurohypophyses. Each white column represents the mean oxytocin content (± S.E., n = 8) found in the incubation medium after a 10 min exposure of a neurohypophysis to a solution containing: choline chloride 100 mM, KCl 56 mM, $CaCl_2$ 2·2 mM, $MgCl_2$ 1 mM, $NaHCO_3$ 6 mM, glucose 10 mM. Oxytocin was estimated in a rat milk-ejection bio-assay. ^{45}Ca uptake was compared in neurohypophyses incubated in this solution, and in control glands exposed to a solution containing 5·6 mM of KCl and 150 mM of choline chloride. Stimulated and control neurohypophyses were washed for 60 min in Locke solution prior to radioactivity measurements. Stippled columns represent the extra radioactivity (mean ± S.E., n = 7) found in the stimulated preparations.

Tetrodotoxin (10^{-7} g/ml), a substance which selectively blocks the sodium channels in axons, affected neither the ^{45}Ca movements nor the evoked neurohypophysial hormone release. The calcium entry which follows depolarization of the squid axon can be separated into an early phase, which is abolished by tetrodotoxin and reflects Ca flowing through the Na channels (Baker, Hodgkin & Ridgway, 1971), and a late phase which is antagonized by Co, Mn, La and D600 (Baker, 1972). Our results show that the calcium influx which leads to neurohypophysial hormone release in response to prolonged membrane depolarization takes place through a permeability channel which appears to be similar to the channel

through which flows the late calcium current described in the squid axon.

This work was supported by the Swiss National Science Foundation and the F. Hoffmann–La Roche Foundation.

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Isolation of human parathyroid hormone and determination of the amino-acid sequence of the amino-terminal part of the molecule

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The effects of a synthetic preparation of gonadotrophin releasing factor on pituitary and ovarian function in anoestrous ewes

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It has been established that a synthetic decapeptide will cause release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in anoestrous ewes. Ovulation was observed in some animals. This led to speculation that the material may have a practical application in controlling ovulation in domestic animals (Reeves, Arimura, Schally, Kragt, Beck & Casey, 1972). No investigations were carried out, however, on post-ovulation ovarian activity resulting from treatment.

The present study was undertaken to assess luteal function in seasonally anoestrous Clun Forest ewes treated with the synthetic decapeptide. In July 1972 blood was taken from jugular vein cannulae in fourteen ewes at intervals of 10 min for 1 hr before, and 5 min for 3 hr after, administration via the cannulae of 150 μg decapeptide (five ewes), 300 μg decapeptide (five ewes), saline or 300 μg of the synthetic tripeptide thyrotrophin releasing factor (four control ewes). Thereafter, samples were taken daily for 25 days. Laparotomies were performed 2–3 days after administration

and the ovaries were examined. Plasma LH content during the initial 4 hr period was assessed and daily plasma progesterone concentrations were determined throughout by radioimmuno-assays (Crighton & Foster, 1972; N. B. Haynes & W. Haresign, unpublished results).

In all sheep given the decapeptide, plasma LH rose after treatment, reached a peak at approximately 110 min and declined thereafter. No LH peaks were observed in control animals. At laparotomy, four animals at each dose level of decapeptide had one apparent ovulation point, macroscopically resembling those seen in normally cycling animals at the same interval after observation of an LH peak. No ovulation points were observed in two treated animals and the four controls. In five treated animals with ovulation points progesterone levels were low throughout and were equivalent to those in control sheep and the two treated animals which had no ovulation points. In three treated sheep with ovulation points progesterone levels rose 2–4 days after administration, indicative of some luteal function, and fell at 10–13 days. The maximum value attained (2·0 ng/ml) was, however, lower than values (3–6 ng/ml) found during the luteal phase of the normal cycle. Laparotomy seemed not to be responsible for reduced progesterone production since three ewes treated with the decapeptide on day 12 of a normal cycle and laparotomized on days 14 and 20, showed normal plasma progesterone levels during the subsequent cycle.

The results demonstrate that administration of the decapeptide caused LH release and ovarian changes characteristic of ovulation in anoestrous ewes. The treatment did not, however, result in normal luteal function.

The authors thank Dr B. J. A. Furr and Dr F. J. Cunningham for progesterone antisera and Mr J. Best of Hoechst Pharmaceuticals Ltd. for the synthetic peptides.

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Factors affecting the viability of heart muscle exposed to anoxia and subsequent reoxygenation

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The effect of hyperbaric oxygen on myocardial blood flow and oxygen consumption following acute coronary artery ligation

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There have been several studies claiming a beneficial effect of hyperbaric oxygen (OHP) in clinical and experimental myocardial infarction (Ashfield & Gavey, 1969; Kline, Marano, Johnson, Goodman, Jacobson & Kuhn, 1970), the assumption being that, because of the considerable increase in physically dissolved oxygen, the amount of oxygen available to the ischaemic regions is increased. This may not be so since, in dogs subjected to haemorrhage, the increase in dissolved oxygen is counteracted by oxygen-induced coronary vasoconstriction and myocardial oxygen availability is not increased (Ledingham, Parratt, Smith & Vance, 1971). The purpose of the present study was to examine the effects of oxygen at two atmospheres' pressure (OHP) in a preparation that enabled blood flow, oxygen availability and oxygen consumption to be measured in both ischaemic and normal regions of the canine myocardium. All the experiments were performed in one of the pressure chambers at the Western Infirmary.

Twenty greyhounds were anaesthetized with trichlorethylene and prepared as previously described (Fisher, Heimbach, Ledingham, Marshall & Parratt, 1973; Parratt, Ledingham & McArdle, 1973). All the dogs initially breathed an air mixture (arterial P_{O_2} 103 ± 5 mm Hg) which, in ten of the dogs, was changed to oxygen (arterial P_{O_2} 1051 ± 39 mm Hg) at least 30 min before ligation of the anterior descending branch of the left coronary artery. In both groups, cardiac output and cardiac work declined to the same extent after ligation, left ventricular end-diastolic pressure was increased and there were no significant changes in blood flow, oxygen availability (blood flow × arterial oxygen content) or oxygen extraction in normal areas of the myocardium. Infarct blood flow 1–2 hr after ligation was significantly lower in the OHP group (12 ± 2 ml./100 g.min) than in the air group (19 ± 2 ml./100 g.min) but there was no difference in either oxygen availability ($4{\cdot}2 \pm 0{\cdot}6$ ml./100 g.min on air and $3{\cdot}8 \pm 1{\cdot}0$ on OHP) or in infarct oxygen consumption ($2{\cdot}2 \pm 0{\cdot}4$ ml./100 g.min for both groups). There was, however, a significant difference between the two groups in the handling of lactate. Before ligation, lactate was extracted by the areas of the left ventricular wall drained by the coronary sinus and the left interventricular vein. Following ligation, lactate was still extracted by the normal myocardium in both experimental groups but was produced by the ischaemic areas. Extraction in the air group, in the area drained by the

interventricular vein, had shifted from $32 \pm 5\%$ to $-14 \pm 12\%$ after 30 min and to $+6 \pm 12\%$ after 1 hr. The corresponding values on OHP were 41 ± 4, -22 ± 4 and $-45 \pm 18\%$. The evidence from these experiments is that OHP alone does not increase oxygen availability to the acutely ischaemic myocardium, nor does it beneficially modify the shift in these areas from aerobic to anaerobic metabolism.

We are grateful to the Scottish Hospitals Endowments Research Trust for financial assistance.

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A comparison of the control of intracellular pH in cardiac and skeletal muscle

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Protein turnover in cardiac and skeletal muscle

BY P. J. GARLICK, D. J. MILLWARD and J. C. WATERLOW. *Department of Human Nutrition, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT*

The rate of protein turnover in rat heart and skeletal (gastrocnemius) muscle has been determined by constant intravenous infusion of [^{14}C]tyrosine (Waterlow & Stephen, 1968; Garlick & Marshall, 1972) and by measurements of the rate of decay of [^{14}C](carboxyl)-labelled glutamate and aspartate (Millward, 1970). Skeletal muscle proteins are renewed relatively slowly, at a rate of 10% per day, compared with the rate in liver and kidney (50% per day) and in brain (17% per day). In heart, protein renewal is almost twice as rapid as in skeletal muscle.

The difference between cardiac and skeletal muscle is also reflected in the turnover of the myofibrils. Those isolated from skeletal muscle have a fractional rate of breakdown of 3% per day compared with 7% in the heart. Thus, the slow turnover of these proteins, which constitute two-thirds of total skeletal muscle protein and one-half of that in heart, is in part responsible for the slow rate of renewal observed in the tissue as a

whole. When the turnover of non-myofibrillar protein in muscle is compared with that of similar proteins from other tissues the difference is still apparent. For example, mitochondria isolated from skeletal muscle are renewed less rapidly than those from liver.

Turnover implies both synthesis and break-down, and growth can occur when protein synthesis is in excess. We have investigated whether this excess of synthesis results from an increase in synthesis or a decrease in break-down. Our results suggest that in normal young rats, variations in the growth rate correlate with differences in the rate of protein synthesis.

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The effect of isoprenaline on cyclic AMP concentrations in skeletal muscle

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The demonstration (*a*) that adrenaline and isoprenaline significantly increased the rate of relaxation of slow contracting muscles in the cat (Bowman & Zaimis, 1958) and of the calf muscle in man (Marsden & Meadows, 1970) and (*b*) that β-adrenoceptor blocking drugs prevented this effect, led us to think that the increase in the rate of relaxation of slow contracting fibres might be brought about by the stimulation of the adenyl cyclase–cyclic AMP system. It was decided, therefore, to correlate the effect of isoprenaline on the rate of relaxation with its effect on cyclic AMP concentrations.

In nineteen cats, the effects of isoprenaline were studied (*a*) on the time course of the contractions of a fast (tibialis anterior) and a slow (soleus) muscle; and (*b*) on cyclic AMP concentrations. Cyclic AMP was assayed by the method of Brown, Albano, Ekins, Sgherzi & Tampion (1971).

The results obtained (Fig. 1) demonstrate that the administration of isoprenaline was followed by a significant increase in the cyclic AMP concentration in both soleus and tibialis muscles. In contrast to these biochemical results, however, isoprenaline altered the time course of the contraction of the two muscles in opposite directions. In the soleus, the time to peak tension and the duration of the contraction were reduced and the rate of relaxation markedly increased; in the tibialis anterior both the time to peak tension and the duration of the whole twitch were increased.

* I wish to thank the Wellcome Trust for support for A. S.

Propranolol completely inhibited all the responses to isoprenaline. These observations suggest that changes in relaxation time do not correlate *per se* with the increase in cyclic AMP concentration in response to isoprenaline.

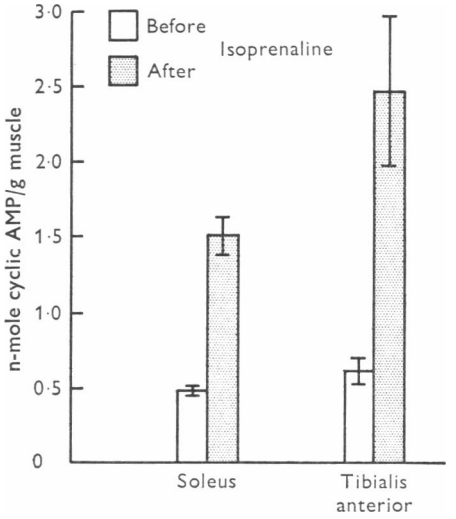

Fig. 1. Cat. Chloralose anaesthesia. Effect of isoprenaline on cyclic AMP concentration in the soleus and tibialis muscles. Isoprenaline was infused intravenously (1 μg/min for 3 min).

Other chemical and physical events may follow the increase in cyclic AMP; for example, the concentration of Ca^{2+} released through the activation of the adenyl cyclase–cyclic AMP system or its subsequent transference from one site of the cell to another, may vary according to the type of skeletal muscle.

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Circulatory and ventilatory adaptations at the start of exercise in normal subjects and patients with chronic obstructive bronchitis

BY R. H. T. EDWARDS, H. L. HAHN, N. B. PRIDE and S. G. SPIRO. *Department of Medicine, Royal Postgraduate Medical School, London W12 0HS*

The effects of hypoxia in the reflex respiratory response to induced oscillations of alveolar P_{CO_2} in man

By D. J. C. Cunningham, K. R. Lyen, G. A. D. McPherson, R. H. K. Marsh* and S. B. Pearson.* *University Laboratory of Physiology, Oxford*

Alternate breaths of inspiratory gas mixtures rich and poor in CO_2 have no special effect on mean ventilation in man (Cunningham, Elliott, Lloyd, Miller & Young, 1965*a*). We have now investigated their effects on breath-by-breath ventilation, measured by open-circuit spirometry (Cunningham, Lloyd, Miller, Spurr & Young, 1965*b*). This work will be published fully (Marsh *et al.* 1973).

Two independently variable gas mixtures were supplied as inspirates to give end-tidal P_{CO_2} of about 39 and 49 Torr in alternate expirates, the lower level being probably above any CO_2 threshold. Inspired and especially alveolar P_{O_2} were held effectively constant, and in each subject measurements were made in both hypoxia and hyperoxia ($P_{A,O_2} \sim 60$ and > 500 Torr). Control determinations in hypoxia were performed in which the switching mechanism was operating but the two gas mixtures were identical.

The six subjects were healthy males of 25 years or less, most of whom had little idea of the nature of the experiments.

When ventilation oscillates in response to breath-by-breath alternation of the stimulus, the direction of change of ventilation from one breath to the next is predictable. Significant oscillation of response was taken to be present when the predictions were fulfilled more often than would be expected on a random basis (Bailey, 1959). Runs of 54–125 breaths were used in the present study.

In eight out of ten tests in which P_{A,CO_2} oscillated in hypoxia there was a significant tendency for ventilation to oscillate breath by breath. Such a tendency was seen in none of the six hyperoxic experimental periods and in only one of the ten control periods. Even in hypoxia the average size of the reflex oscillation was less than 5% of the ventilation.

These results provide further support for the view that in man, unlike the cat, reflex effects of quick changes of P_{A,CO_2} (unless large enough to induce disgust) are demonstrable only when hypoxia is present, a conclusion already firmly based on other work (Cunningham, Lloyd, Miller & Young, 1965*c*; Goode, Brown, Howson & Cunningham, 1969). The results also show that some of the forms of stimulation reported earlier, though without effects on mean ventilation (Cunningham *et al.* 1965*a*) are nevertheless capable of producing reflex responses. It follows that alternate rising and falling stimuli, acting presumably at the arterial chemo-

* M.R.C. Scholar.

receptors, cancel out each other when, as here, they are applied at the same phase of the respiratory cycle. In this respect, the responses of our human subjects differ from those reported for the anaesthetized dogs of Dutton, Fitzgerald & Gross (1968).

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Effect of posture on bronchial dimensions in the dog

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Human foetal breathing *in utero*

BY K. BODDY and C. MANTELL. *The Nuffield Institute for Medical Research. Oxford*

Maternal abdominal wall movements attributed to foetal breathing *in utero* were described by Ahlfeld (1888). This attribution was not generally accepted, first because there was no direct evidence that the movements reflected those of foetal respiratory muscles, and secondly because studies in laboratory animals suggested that foetal breathing *in utero* was not normally present.

Work in sheep (Dawes, Fox, Leduc, Liggins & Richards, 1972) has shown that there is normally foetal breathing *in utero* for about 40 % of the time and related to rapid-eye-movement sleep. Two types of respiratory activity were described. 'Gasping or sighing' recurred irregularly at a slow rate (1–5 per min); 'rapid irregular breathing' consisted of episodes of much higher frequency (1–4 Hz). In sheep the presence of normal foetal breathing was a good indicator of health.

Human foetal chest wall movements *in utero* have been recorded using an ultrasonic A-scan method (Boddy & Robinson, 1971). The movements

are often transmitted through the maternal abdominal wall (Boddy & Mantell, 1972). Foetal breathing has been studied on 200 antenatal patients and on 30 patients in labour. As in the lamb it is episodic. It occurs at a frequency of 30–70 breaths per minute and is normally present for about 65% of the time. In sheep hypoxaemia, hypocapnia, hypoglycaemia and respiratory depressant drugs reduce foetal breathing, while hypercapnia increases its rate and depth. Our observations on the human infant *in utero* suggest similar conclusions. In normal labour breathing movements are reduced. Strong uterine contractions accompanied by evidence of partial foetal asphyxia (from measurements on scalp blood samples and changes in heart rate) were associated with a further reduction of normal foetal breathing and with the appearance of gasping movements. Before the onset of labour in two women a large reduction in foetal breathing and the appearance of deep regular gasping movements heralded intra-uterine death.

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A method for estimating pulmonary capillary blood flow from the rate of change of alveolar CO_2 pressure during rebreathing

BY M. WINSBOROUGH. *The Royal Naval Physiological Laboratory, Alverstoke, Hants.*

Local control of blood flow in lungs of the Coati mundi

BY E. E. DAVIES, B. J. B. GRANT, J. M. B. HUGHES and H. A. JONES. *Department of Medicine, Royal Postgraduate Medical School, London W12 0HS*

The Coati mundi (*Nasua nasua*) is a small mammal, indigenous to Central and Southern America. The lungs of Coatis lack the communications which in other species (dog, cat and man) allow collateral gas flow between neighbouring lobules within a lobe (J. Mead, personal communication). The Coati mundi is a convenient size (2·5–5·0 kg, body weight) for studies in the intact lung of the gas-exchange behaviour of small lung units.

The animals were anaesthetized with 1 % chloralose and 10 % urethane, and placed supine in a plethysmograph with a cannula from a tracheostomy leading to the outside. Breathing was spontaneous. A catheter (80 cm in length, 0·14 cm i.d.) with a bell-shaped tip (0·29–0·35 cm o.d.) was passed down the trachea until it wedged in a bronchus supplying 5–10 secondary lobules of the right or left lower lobe. An inner catheter (0·06 cm o.d.) supplied inspired gas for the lobules at a constant flow rate. Lobule tidal volume was recorded from a miniature spirometer. The mixed expired gas from the lobule (or the lung) was sampled continuously with a mass spectrometer (modified MS 4) and the mean oxygen, carbon dioxide and nitrogen concentrations and respiratory exchange ratio (R) recorded for each 6 sec period.

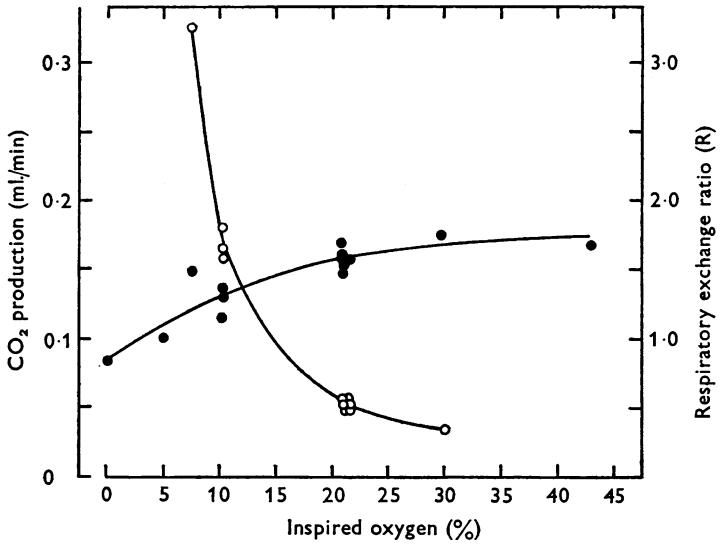

Fig. 1. Lobule CO_2 production (●) ml./min STPD, and respiratory exchange ratio (○) plotted against inspired oxygen concentration. There was no CO_2 in the inspired gas.

Fig. 1 shows an experiment where the inspired oxygen concentration to the lobule was varied from 43 % to zero. During this period overall alveolar ventilation (325–440 ml./min) lung R (0·7–0·78), CO_2 production (11·9–12·9 ml./min), arterial P_{O_2} (101–107 Torr) and the composition of the mixed venous blood remained reasonably constant. Lobule alveolar ventilation varied (4·4–5·7 ml./min), but not systematically with O_2 concentration nor enough to account for the observed changes in lobule $\dot{V}_{CO_2}$ or R. Raising inspired CO_2 to 8 % with constant inspired O_2, reduced lobule $\dot{V}_{O_2}$. Since these lobules formed less than 1 % of the lung these observations suggest

that local adjustments of blood flow occur with changes in lobule P_{O_2} and P_{CO_2} – a control mechanism proposed by von Euler & Liljestrand (1946).

This work was supported in part by the Medical Research Council.

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Energy metabolism during exercise after fenfluramine

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The contribution of leg (muscle plus bone) volume to maximum aerobic power output: the effects of anaemia, malnutrition and physical activity

BY C. T. M. DAVIES. *M.R.C. Environmental Physiology Research Unit, London, W.C. 1*

In a recent series of publications (see Davies, Mbelwa, Crockford & Weiner (1973) for a general review) the close association of maximum aerobic power output ($\dot{V}_{O_2\,max}$) with estimates of leg (muscle plus bone) volume (L.V.) (see Jones & Pearson, 1969), has been demonstrated in children and young healthy adults.

In this communication the relationship of $\dot{V}_{O_2,\,max}$ to L.V. has been analysed in East African children suffering from malnutrition (using the clinical and anthropometric criteria of Jelliffe (1966) and severe iron-deficiency anaemia (Hb < 8·5 g/100 ml.) and in a group of rural adult East Africans engaged in prolonged active daily work. The data have been compared to 'normal' East Africans aged 7–35 years.

The results show that the association of $\dot{V}_{O_2,\,max}$ with L.V. is not causal, the effects of increased habitual activity and anaemia on $\dot{V}_{O_2,\,max}$ are independent of L.V., the former being additive and the latter multiplicative. Further, oral iron therapy produces an increase in $\dot{V}_{O_2,\,max}$ in anaemic subjects towards normal values without a concomitant change in L.V. In malnutrition, however, the relationship of $\dot{V}_{O_2,\,max}$ to L.V. remains unchanged: $\dot{V}_{O_2,\,max}$ decreases *pari passu* with the reduced leg (muscle plus bone) volume.

The analysis gives a clearer understanding of the relationship between 'active' muscle mass and aerobic power output on the bicycle ergometer and suggests that estimates of L.V. may not be used to predict $\dot{V}_{O_2,\,max}$ directly, in populations where the level of habitual activity and disease patterns are unknown. Nevertheless the data could serve as a basis for

clinical diagnosis in the industrial and medical fields particularly for cases of debilitating disease which have an effect on physiological performance and effort tolerance. The results at present cannot be applied to men and women over 35 years of age.

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The role of central and peripheral mechanisms in the maintenance of experimental hypertension in the rabbit

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Action of levodopa on the blood pressure of conscious rabbits

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Changes in the performance of the electrogenic transfer mechanisms of the small intestine related to different sources of a commercial feeding diet for rats

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Levin & Syme (1971) characterized the electrogenic transfer mechanisms of the small intestine for hexoses and amino acids by estimating *in vitro* their 'apparent K_m's' and 'maximum potential differences (p.d.$_{max}$)' from Lineweaver–Burk plots of the transfer potentials generated at various concentrations of the solutes. Hypothyroidism had no effect on the 'apparent K_m' for electrogenic valine transfer but did enhance its p.d.$_{max}$ by 41 % compared to euthyroid intestine. These data agreed with lack of change of K_m but enhanced valine transfer maximum observed previously by chemical methods (London & Segal, 1967).

The rats in our original experiments were fed Diet 86 manufactured by Burnhill, Cleckheaton. On repeating the experiments a year later no significant increase in the p.d.$_{max}$ for valine during hypothyroidism could be obtained. Examination of the data showed, however, that the p.d.$_{max}$ of the euthyroid controls had increased significantly compared to the previous euthyroid control value and the p.d.$_{max}$ of the hypothyroid group had fallen compared to previous values. Our suspicions were aroused that there had been a change in the diet. Investigations revealed that Diet 86

was now being obtained from a new supplier, Oxoid, London. We thought that Oxoid 86 was influencing the thyroid status of the euthyroid rats and was raising their $p.d._{max}$ closer to the hypothyroid level. To test this hypothesis another group of rats were fed Burnhill 86. The $p.d._{max}$ values obtained for electrogenic valine transfer in this group were indeed significantly lower than those of rats fed Oxoid 86.

Estimations of total iodine in the diets revealed that Burnhill 86 contained $1{\cdot}2 \pm 0{\cdot}2$ μg/g (mean $\pm$ S.E. $n = 10$) compared to $0{\cdot}6 \pm 0{\cdot}09$ μg/g of Oxoid 86 (personal communication G. D. Broadhead). The thyroid uptakes of intraperitoneally injected ^{131}I were less in rats fed Oxoid than in those fed Burnhill 86, evidence that the Oxoid diet contained an agent(s) that affected the iodine trapping mechanism of the thyroid. These factors may be part explanation of the 'hypothyroid-mimicking' effects of the Oxoid 86 diet. Despite these effects, however, the oxygen consumption of the rats on the two diets was not significantly different.

Feeding supplementary iodine in the drinking water (3 μmoles and 9 μmoles KI/l. water) for ten days to rats on Oxoid 86 reduced the $p.d._{max}$ for valine transfer but had no effect on that measured in rats fed Burnhill 86.

Thus feeding two nominally similar commercial diets 86 can significantly affect the performance of an electrogenic transfer system of the small intestine, probably indirectly by alterations in iodine and thyroid balance. Intestinal function in this instance is more sensitive to such changes than total body oxygen consumption.

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Glyceride-fatty acid and free fatty acid uptake by human adipose tissue in obesity

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Uncoupled Na efflux through the Na pump

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Human red cells incubated in a Na- and K-free medium show a relatively large ouabain-sensitive Na efflux. Small concentrations of Na in the

medium (1–5 mM), which decrease the affinity for external K, inhibit this efflux to a variable extent suggesting some sort of Na–K exchange. An exchange of Na for K leaking out of the cells is unlikely since ouabain has no effect on the K loss (Garrahan & Glynn, 1967). The ouabain-sensitive Na efflux could still represent a kind of Na–K exchange if Na could be expelled simultaneously with the operation of a K shuttle at each pump site, internal K moving backwards and forwards without actually being released to the medium. The outward Na movement would then be coupled to the inward translocation of unreleased K.

In order to test this hypothesis and to investigate this effect further, we measured the ouabain-sensitive Na loss from either intact cells or hypotonically resealed ghosts under a variety of conditions. We found that:

(1) While inosine greatly reduced the ouabain-sensitive K loss from intact cells (Glynn, Lew & Lüthi, 1970), the ouabain-sensitive Na loss into Na- and K-free media was the same as in glucose-fed cells.

(2) In hypotonically resealed ghosts containing about 10 mM-Na, 2 mM-ATP, 3 mM-Mg, 1 mM phosphate, 30–40 mM choline chloride and K, from 0·76 mM ($[K]_o < 1\ \mu M$) to 10 mM ($[K]_o < 7\ \mu M$), incubated for 1 hr at 37° C, the ouabain-sensitive fraction of ^{24}Na lost ($k = 0{\cdot}026 \pm 0{\cdot}003\ hr^{-1}$) was independent of $[K]_i$, the internal K_m for K being about 10 mM under similar conditions (Simons, 1972).

(3) At $[Na]_o < 18\ \mu M$, the ouabain-sensitive Na loss from hypotonically resealed ghosts, into a choline chloride-Tris medium, saturated with increasing $[K]_o$ (from 1 μM to 10 mM) and was half maximal at about 0·10 mM-K. The addition of 5 mM-Na to the medium decreased the ouabain-sensitive Na loss by about the same amount at $[K]_o = 1\ \mu M$ and at $[K]_o = 10$ mM (95% and 10% inhibition, respectively).

(4) ATP but not ADP is required inside the cells to sustain the ouabain-sensitive loss of Na into Na- and K-free media.

(5) The ouabain-sensitive Na loss is largely independent of the salt used to replace the normal Na and K salts in the medium ($MgCl_2$, choline chloride, Tris-Cl, $MgCl_2$ + sucrose).

The ouabain-sensitive Na loss into Na- and K-free media, therefore, does not seem to be coupled with any form of K movement. The general similarity of this flux with the normal Na–K exchange suggests that it is probably associated with some spontaneous dephosphorylation of the Na pump which does not involve the inward translocation of a cation.

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Factors promoting intestinal hyperplasia in lactating rats

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Premature cessation of macromolecule uptake by the young rat intestine following thyroxine administration

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The small intestine of the young rat is able to absorb macromolecules including maternal antibodies from milk for 18–22 days after birth. Timing of the cessation of macromolecular absorption (closure) is known to be influenced by several factors including the secretions of the adrenal cortex (Buchanan-Lee, Clarke & Hardy, 1972; Daniels, 1972; Daniels & Hardy, 1972; Daniels, Hardy, Malinowska & Nathanielsz, 1972). Since administration of thyroxine has been shown to accelerate several aspects of maturation in the young rat (Schapiro & Norman, 1967), the effect of such treatment on the time of closure has also been investigated.

Experimental animals were injected subcutaneously from the 5th postnatal day with a solution of thyroxine in saline (2·0 μg thyroxine/g body wt. day). Litter-mate controls were injected with saline only. Animals were sacrificed on days 9, 11, 12 or 13 and the [^{125}I]P.V.P. uptake was determined as described previously (Clarke & Hardy, 1969).

Fig. 1 shows that thyroxine administration resulted in premature closure of the small intestine after a delay of 4–5 days. The time course of thyroxine induced closure was very similar to that of normal closure (Clarke & Hardy, 1969). Furthermore, histological examination revealed a comparable progressive displacement of vacuolated cells from the villi of the terminal small intestine.

After 4 days of similar thyroxine treatment in the neonatal rat Schapiro & Norman (1967) demonstrated a maturation of the pituitary-adrenal response to stress. The possibility that the present effect of thyroxine on the small intestine is secondary to an increased secretion of adrenal corticosteroids is at present being investigated.

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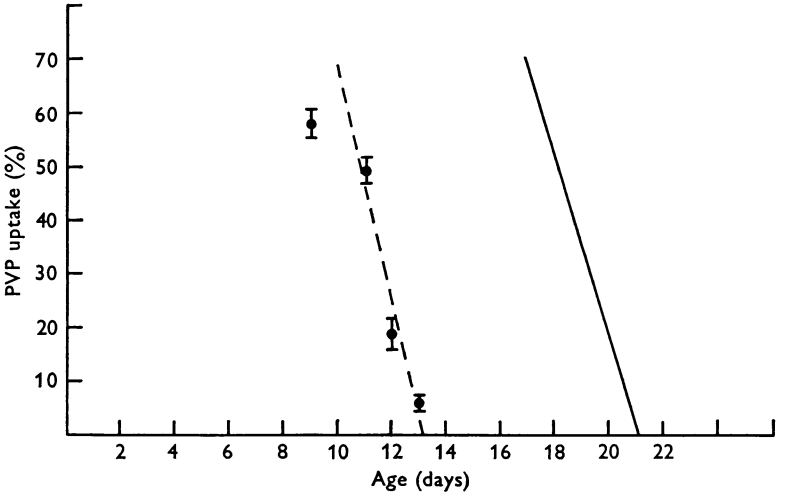

Fig. 1. The effect of administration of exogenous thyroxine on the uptake of [^{125}I]PVP by the small intestine of young rats. ● represents the mean, ± the S.E. of mean for rats given thyroxine. The dotted line is the best fit by the method of least squares for the results from animals tested on days 11, 12, 13. The solid line represents the regression line for normal animals (Clarke & Hardy, 1969).

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Comparative release of enterokinase and other small intestinal enzymes following secretin and pancreozymin in man

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Psychometric performance: Circadian rhythms and effect of raising body temperature

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Both temperature and psychometric performance vary circadianly (Kleitman, 1963), and in many tests performance is best when temperature is highest. It has previously been shown (Fort, Gabbay, Jackett, Jones, Jones & Mills, 1971) that artificially lowering body temperature from its circadian peak reduced performance scores; the relationship between temperature and performance was similar, whether the temperature changes were part of the natural circadian rhythm or were artificially induced.

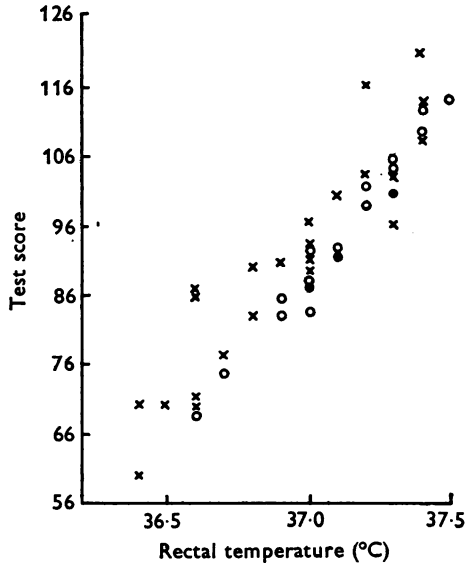

Fig. 1. Relationship between performance on aiming test and rectal temperature. ×, Spontaneous variation of temperature over the 24 hr; ○, temperature raised by hot bath; ●, temperature raised by exercise.

We have now attempted the converse experiment, by artificially warming subjects at times when temperature was low. This was usually achieved by immersion to the waist in water at 39–44° C. In a few additional observations on two subjects temperature was also raised by vigorous exercise, standing running.

Four subjects, one male and three females, carried out five different simple psychometric tests; a fifth subject, male, performed three tests only. Each subject performed each test 14–26 times at different hours at

his 'natural' temperature, and 6–18 times on one to three occasions when temperature was raised artificially.

Fig. 1 shows data on maximum tapping rate from one subject. In this, as in all other plots of performance against rectal temperature, for every subject, the relationship between score and body temperature was indistinguishable whether the temperature changes were spontaneous or artificially induced.

The numerical value of all correlation coefficients between performance and temperature lay between 0·516 and 0·980; P was always below 0·01 and usually below 0·001.

Of the two tests common to this and the previous (Fort *et al.* 1971) series, one failed in the previous series to show significant correlation with temperature. For the other, accurate performance in the aiming test, regression coefficients upon temperature were, for most subjects, of similar magnitude: in the earlier series 12·8, 12·7 and 8·5 and in the present series 12·7, 15·4, 13·9, and 44·0 points min^{-1} $°C^{-1}$.

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Experimental expansion of the bile acid pool

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Sensitivity of nerve endings to changes of osmolarity in the perfused rabbit liver

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Rabbit livers were perfused at 37° C via the portal vein with Krebs solution at a controlled rate of about 1·5 ml./min.g wet wt. tissue, the method being based on that of Andrews & Stratmann (1968). Fine bundles of hepatic nerves were dissected out and placed across wick electrodes. Action potentials were monitored for changes in frequency and pattern of discharge. In some experiments variations were made in the concentration of the Krebs solution, the ratio of ion concentrations being kept constant, but the total molarity varied. In other experiments various substances were added to the Krebs solution.

Niijima (1969) described 'osmoreceptors' in guinea-pig livers perfused with Ringer solution at 30° C and the high portal pressure of 50 cm saline. Variations of 20 m-osmole/l. of sodium chloride altered the rate of nerve discharge. Such sensitive receptors were not found in our study. First, no effect was observed when the concentration of the Krebs solution was varied between 285 and 316 m-osmole/l. Secondly, more than 100 nerve bundles in 10 livers were studied after addition of 17 m-osmole of sodium chloride and in only three bundles was there a perceptible increase of nerve activity. When double this amount of sodium chloride was added more nerves which reacted were seen, but the number remained small.

The effect of varying the colloidal osmotic pressure was also investigated by perfusing with Krebs solution in which substances with large molecules had been dissolved. A small but appreciable number of nerve bundles were stimulated by dextran, mol. wt. 110000, and polyvinyl-pyrrolidone (PVP), mol. wt. 44000, at physiological oncotic pressures as well as bovine serum. The action potentials were of low voltage and single fibre preparations were not obtained, but the same nerve bundles reacted to all three fluids. It is thought that the important factor was a property of the reactive nerve fibres rather than a similarity in the chemical composition of the stimulating substances. Changes of oncotic pressure within the physiological range produced alterations in the rate of firing. There was a marked difference in the frequency of nerve discharge with dextran 110000 at 38, 40 and 42 g/l. corresponding to steps of oncotic pressure of under 2 mm Hg. Nerve bundles which reacted to changes in oncotic pressure were unaffected by changes of intrahepatic hydrostatic pressure and variations in the viscosity of the perfusion fluid, and it is, therefore, unlikely that the effect of the bovine serum, the PVP 44000 and dextran 110000 was mediated through mechanoreceptors. It would appear that certain nerves in the rabbit liver are affected by small changes of oncotic pressure.

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The effect of lead on α and β chain synthesis *in vitro* and *in vivo*

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The effect of plasma sodium concentration on the urinary excretion of sodium in anaesthetized dogs

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Renal sodium excretion (U_{Na} V) is regulated by many factors. Of these plasma sodium concentration (P_{Na}) and glomerular filtration rate (GFR) are of special interest since they determine the filtered load of sodium (F_{Na}).

The relationship between these factors was studied in 37 greyhounds anaesthetized with pentobarbitone and artificially ventilated. Observations were first made during a systemic infusion of 0·9 % NaCl solution at 2–4 ml. min.$^{-1}$. The sodium concentration of the infusion was then increased to 3·6–7·2 % or reduced to 0·45 %; its rate was not altered. In eleven experiments P_{Na} was reduced by haemodialysis against a hypotonic solution. GFR was estimated as the clearance of ^{125}I Na-diatrizoate. Sodium concentration was measured by flame photometry.

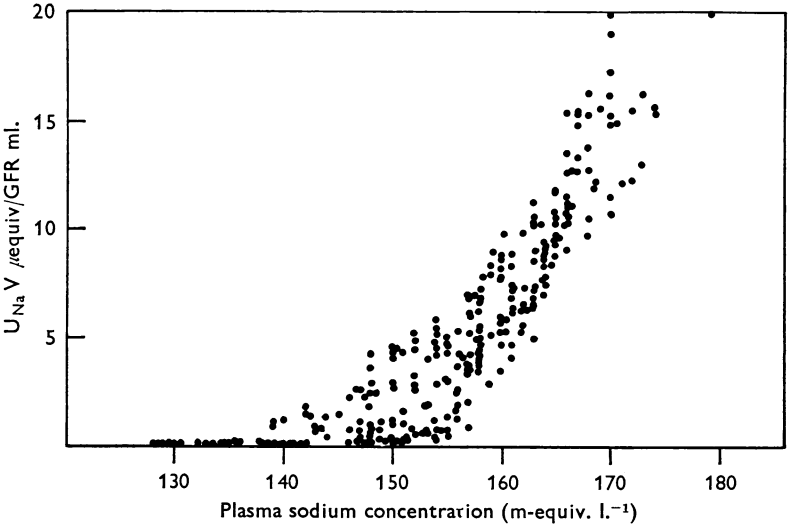

Fig. 1. Collected data showing the relationship between sodium excretion per unit of glomerular filtrate ($U_{Na}V$/GFR) and plasma concentration of sodium.

At sodium concentration less than 140 m-equiv. l.$^{-1}$ sodium excretion bore no relation to F_{Na} and was always very low. Above 140 m-equiv. l.$^{-1}$ sodium excretion rose linearly with F_{Na}. The slope of this rise increased as plasma sodium increased. When the relationship between sodium excretion and GFR was examined, once more a linear relation was found which again

varied with P_{Na} values above 140 m-equiv. $l.^{-1}$. The respective contributions of P_{Na} and GFR to sodium excretion in the different P_{Na} ranges was assessed from these results. The variation in sodium excretion produced by a change in F_{Na} was compared with that predicted to occur if an identical change in F_{Na} were produced by GFR alone. The difference between these two must reflect the sodium excretion attributable to P_{Na} itself. It was found that GFR could only account for sodium excretion between P_{Na} levels of 140 and 150 m-equiv. $l.^{-1}$. At higher levels P_{Na} had a dominant effect on sodium excretion. Whatever the rate of glomerular filtration, small increments in P_{Na} were then always accompanied by large increments in sodium excretion (Fig. 1).

The effect of nicotinic acid on the synthesis of plasma lipoproteins in monkeys

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Responses of aged men to passive heating

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The physiological responses to heat stress in a group of aged male subjects were compared with a group of young adult controls. Ten aged men (aged 65–89 years), all healthy ambulant independent in-patients of a local authority hostel, and eight male medical students (20–24 years) were the subjects of this study.

The thermal stress consisted of immersion of one hand in a water bath at 42° C for 60 min whilst lightly clad and seated comfortably in a climatic chamber at an ambient temperature 26–27° C (wet bulb globe thermometer 22–23° C). The standard study duration was 2 hr, starting 30 min before and ending 30 min after immersion. During this time, finger blood flow was measured every 2 min by venous occlusion plethysmography in each of two fingers of the non-immersed hand. Sweat rate on the anterior chest wall was continuously recorded by a ventilated capsule, and mean skin temperature was computed every 5 min using a modification of Burton's 3-point formula (1934).

In all subjects there was a significant ($P < 0{\cdot}001$) rise in core temperature (T_c) as measured by thermistor at the tympanic membrane. The mean pre-immersion T_c was lower in the aged (36·98° C) than in the young (37·04° C) but was not statistically significantly different. The extent of the rise in T_c during hot immersion was significantly greater ($P < 0{\cdot}001$) in the aged ($0{\cdot}57 \pm 0{\cdot}17$° C) than in the young ($0{\cdot}19 \pm 0{\cdot}14$° C). The time

taken for T_c to reach its maximum was significantly greater ($P < 0.001$) in the aged (45.9 ± 9.1 min) than in the young (34.4 ± 10.57 min), but the rate of rise was also greater (0·012° C/min) in the aged compared with (0·005° C/min) in the young. Thus the net rate of heat uptake was greater in the aged.

T_c thresholds for vasodilatation (T_{vd}) and for sweating (T_{sw}) were calculated. There was not a statistically significant difference in T_{vd} between the aged and young groups. A significant ($P < 0.01$) difference in T_{sw} was shown in the aged group (37.67 ± 0.25° C) as against (37.15 ± 0.12° C) in the young group. This elevated sweating threshold probably accounts for the greater lability of core temperature in the aged.

W. H. F. was an Ainsworth Scholar (N.U.I.) and Fellow of the Medical Research Council of Ireland during this study. Both authors are grateful to the Biomedical Research Trust for financial help.

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Effect of drugs which cause megaloblastosis on the free intracellular pools of DNA precursors

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Evidence that the noradrenergic innervation of the cerebral cortex is necessary for learning

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The fine network of noradrenaline-containing nerve terminals in the cerebral cortex is derived from cell bodies of the nucleus locus coeruleus in the floor of the fourth ventricle (Ungerstedt, 1971). Electrical self-stimulation behaviour can be obtained with electrode tips placed close to the locus coeruleus (Arbuthnott, Crow & Spear, 1970; Crow, Spear & Arbuthnott, 1972). This finding is consistent with hypotheses (Crow, 1968; Crow & Arbuthnott, 1972) that the noradrenergic terminals in the cortex function as a 'reinforcement' system, and a further implication of such hypotheses is that the locus coeruleus system is involved in the physiological mechanisms of learning.

In these experiments we investigated the effects of bilateral ablation of the nucleus locus coeruleus, in rats, on a simple test of learning capacity and on cortical noradrenaline levels. A group of rats with electrolytic

lesions in the region of the locus coeruleus were compared with groups with bilateral cerebellar and bilateral deep brain-stem lesions, and with a group with burr holes alone. All rats were starved to 90% body weight and given five trials for a food reward in an L-shaped runway on each of 16 days, the speed of running in the initial arm of the runway being assessed with a photo-cell device. The brains were removed, the noradrenaline content of the cerebral cortices assayed fluorimetrically, and the brain-stem–cerebellar regions prepared for histological examination.

After examination of the histological material a group of six rats with complete or nearly complete bilateral ablations of the nucleus locus coeruleus were selected from the total group of twenty-eight rats with lesions aimed at this nucleus. This group of six rats was compared with the six rats in the three control groups. Cortical noradrenaline content was significantly reduced (locus coeruleus lesioned group 102 ± 24 ng/g: controls 325 ± 31 ng/g; $P < 0{\cdot}001$). The mean latencies in the runway situation showed a rapid decrease in running time in each of the three control groups in the first 5 days of testing but the rats with locus coeruleus lesions took much longer to learn the task, and did not reach the level of performance of the controls within the 16-day test period (analysis of variance $F = 19{\cdot}629$, d.f. 3/20, $P < 0{\cdot}001$). In three rats with virtually complete ablations of the nucleus locus coeruleus, learning, as assessed in this experimental situation, was absent. Such rats did, however, show normal rates of weight gain and exploratory activity and did not show signs of motor defect.

These experiments suggest that the noradrenergic innervation of the cerebral cortex is necessary for learning (Crow, 1968; Kety, 1970). The results of these experiments and of those on electrical self-stimulation (Arbuthnott *et al.* 1970; Crow *et al.* 1972) are consistent with the concept that the noradrenaline-containing neural system arising from the nucleus locus coeruleus functions as a 'reinforcement' system which acts to signal the results of successful motor activities, and thereby to ensure that these behaviours are learned (Crow, 1968; Crow & Arbuthnott, 1972; Crow, 1973).

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Factors influencing the aberrant reinnervation of axotomized submandibular sympathetic trunks by parasympathetic nerves in cats

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Superior cervical ganglionectomy causes degeneration of the submandibular sympathetic trunk with permanent loss of its adrenergic nerves, but in time a partial retrograde reinnervation occurs by sprouting from parasympathetic nerves in the gland (Garrett, 1969, 1971). The trunks then show strong cholinesterase staining and absence of catecholamine fluorescence. The effects of different denervation procedures on the events occurring in the submandibular sympathetic trunks have now been studied by histochemistry and electron microscopy.

Simple axotomy of the trunk caused extensive degeneration distally and occasionally there was a total loss of adrenergic nerves in the gland. If, however, adrenergic sprouts were able to grow into the distal segment of the trunk, partial recovery of adrenergic nerves occurred and the retrograde parasympathetic reinnervation of the trunk was inhibited. In some experiments the external carotid artery, together with the accompanying submandibular sympathetic trunk, was ligatured between the lingual and submandibular arteries and then sectioned. This did not always remove all the adrenergic nerves in the gland but it prevented the adrenergic reinnervation of the distal trunk, and a retrograde parasympathetic reinnervation occurred, as after ganglionectomy. Excision of the chorda at the time of superior cervical ganglionectomy did not hinder the aberrant parasympathetic reinnervation of the trunk and indicates that the postganglionic sprouting will occur in the absence of preganglionic impulses. In a number of cases after ligature and section of the external carotid artery, as above, the proximal sympathetic trunk was sutured to the distal end of the transected chorda. Growth of adrenergic axons occurred along the chorda in each case and in time there was a dense reinnervation of the gland by adrenergic nerves. This, however, did not stop the retrograde parasympathetic reinnervation of the distal part of the submandibular sympathetic trunk, and suggests that a time factor is involved: thus, if adrenergic nerves are to inhibit the parasympathetic sprouting down the trunk they must reach there first. There were perhaps fewer parasympathetic nerves in the distal sympathetic trunks after this procedure than when the proximal sympathetic trunk was not sutured to the chorda. It is concluded that when one type of nerve has grown down the trunk it inhibits the growth there of the alternative type of nerve, but the mechanisms inducing or suppressing the sprouting are unknown.

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The effect of dietary fat on platelet function

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Potentiation of platelet aggregation and adhesion by heparin both *in vivo* and *in vitro*

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