points. When the latter mean was equated to 100% for three such experiments, the average of the 0800 and 1200 values was higher, by 21, 43, and 43% respectively, than the mean of the remainder of values. In the first experiment depicted in Figure 1, values were based on adrenal incubation with only a single pool of pituitaries at each time point. A second and third experiment which gave comparable results, involved several pituitary pools at each time point and the corresponding P values for the latter experiments were 0.013 and 0.036.

The present studies and different earlier work[1] both explore complementary facets of the *in vivo* timing of spontaneous pituitary-adrenal interactions by an *in vitro* approach. Continuance of such *in vitro* investigation will serve to examine in further detail the periodic interactions of pituitary and adrenal factors, in the absence of complicating effects, e.g., from other hormonal, neural or circulatory controls. Such work may then serve for a more rigorous analysis of related observations and postulates on the adrenal cycle based upon *in vivo* work exclusively[2,3,13,14].

In any event, the *in vitro* approaches show that the reactivity of the adrenal to ACTH, on the one hand, and the adrenocorticotropic activity of the pituitary, on the other, both function periodically in a predictable fashion under standardized conditions, and, also, that these two rhythms do not peak simultaneously[4]. Figure 2 visualizes this point. The parameters of pituitary-adrenal function studied reveal the same frequency. Important differences-in-phase among these circadian periodic functions are also apparent.

All data shown in Figure 2 were converted first into a percentage of the mean for a given series. The means of these relative values plotted against time for three experiments involving the pituitary incubations with adrenals (------) are compared with those for serum corticosterone and adrenal responsiveness to ACTH tested *in vitro* as documented earlier[1] in the same strain of mice and under the same conditions. In the C mice studied, all three functions show clearly a circadian rhythm. Circadian periodic adrenocorticotropic activity of the C mouse pituitary leads-in-phase the rhythm in serum corticosterone which, in turn, is about 180° out-of-phase with the rhythm in adrenal reactivity to ACTH added *in vitro*.

Further work will have to be done before possible rhythms in hormone production and/or release can be segregated from the contribution of changes in hypophyseal ACTH content as such to the pituitary adrenocorticotropic rhythm here reported. Further questions deserving added study in themselves relate to the degree of generality of pituitary adrenocorticotropic rhythm and to its time relations in other strains or species. Nevertheless, these *in vitro* data as a whole reveal a set of interesting temporal parameters for students of pituitary-adrenal physiology and related bioassays.

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Zusammenfassung. Ein circadianer Rhythmus in der adrenocorticotropen Wirkung der Hypophyse bei Inzucht-C-Mäusen wird durch ein *in vitro*-Verfahren nachgewiesen. Es werden Angaben der Phasenunterschiede zwischen dem hypophysären Rhythmus und den gleichfalls circadian-periodischen Schwankungen gemacht: (1) im Serum-Corticosteron und (2) in der Reaktion der Nebenniere auf ACTH, *in vitro*.

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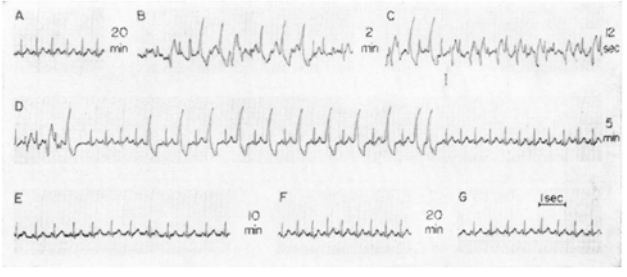
Antiarrhythmic Action of Synthetic Oxytocin in Anesthetized Man

The purpose of this communication is to present preliminary work on the use of synthetic oxytocin (Syntocinon®) in the treatment of electrocardiographically observed ventricular arrhythmias occurring under general anesthesia. Ten patients, eight of whom were anesthetized with halothane and two with methoxyfluorane were studied. The arrhythmias observed were frequent premature ventricular contractions (three patients), bigeminy (five patients) and multifocal ventricular contractions (two patients). The arrhythmias were associated with endotracheal intubation (two cases), carbon dioxide retention (one case), attempted coughing in response to the endotracheal tube (two cases), breath holding (one case), and adrenal manipulation (two cases). In two cases the etiology of the arrhythmia was not known.

The rapid intravenous infusion of 10 U of synthetic oxytocin restored normal sinus rhythm in seven cases while 20 U was required in one case. Conversion of the arrhythmias occurred within 30–60 sec. Figure 1 shows a representative case. In two cases a total dose of 20 U of synthetic oxytocin had no effect on the arrhythmia. A rise in pulse rate of 10–20 beats per min was observed in three patients and lasted 60–90 sec. In five patients a fall in mean arterial blood pressure of 15–20 mm Hg was observed (60 sec duration).



Lead 2 of electrocardiogram during halothane anesthesia in a 62 year old male. (A) Control record after 30 min of anesthesia. Normal sinus rhythm. (B) Ventricular arrhythmia associated with adrenal manipulation. (C) 2 min later, arrhythmia still present. At arrow 10 units of synthetic oxytocin given intravenously. (D) Normal sinus rhythm 33 sec after synthetic oxytocin infused. (E) (F) (G) Normal sinus rhythm during remainder of operation.

Synthetic oxytocin was previously shown to afford protection against epinephrine induced arrhythmias under cyclopropane and trichlorethylene anesthesia in the dog[1]. PANISSET and BEAULNES[2] demonstrated an antiarrhythmic action on (1) atrial arrhythmias induced in isolated rabbit atria by electrical stimulation, administration of acetylcholine and lowering of potassium concentration, (2) ventricular arrhythmias produced by electrical stimulation of the isolated perfused rabbit heart, (3) chloroform-epinephrine induced cardia arrhythmias in the dog. BIRCHER, KANAI, and WANG[3] were able to convert ventricular arrhythmias induced by pentylenetetrazol administered intravenously in the dog, but not when pentylenetetrazol was injected into the fourth ventricale. The antiarrhythmic action has been attributed to a quinidine-like property of the molecule bringing about cell membrane permeability changes[2], or to an inhibition of oxidative metabolism[4,5].

Zusammenfassung. Synthetisches Oxytocin wurde für die Behandlung von ventrikulären Arrhythmien, welche bei Patienten im Lauf einer Allgemeinnarkose aufgetreten sind, verwendet. In 8 von 10 Fällen erfolgte eine prompte Wiederherstellung des normalen Sinusrhythmus. Es konnten keine unerwünschten kardiovaskulären Wirkungen beobachtet werden.

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The Effect of Bradykinin on Blood Flow and Heat Production in the Myocardium

The use of 'internal calorimetry' in the evaluation of blood flow in rabbit myocardium has already been described[1]. Its use in the evaluation of heat production changes in other tissues has also been described[2]. The technique uses a heated thermocouple which can be implanted in the myocardial muscle mass with little trauma. Measurements are of the difference between the apparent thermal conductivity of the living myocardium and the thermal conductivity of the dead myocardium (which has been shown to be an approximate linear function of blood flow in any likely biological range of flow) and of corrected temperature, i.e. myocardial temperature recorded with the 'cold junction' in the aorta and corrected for changes due solely to blood flow change. In so far as heat losses are constant and alterations in blood temperature are automatically compensated by the cold junction, the remaining changes are regarded as due to alterations in local heat production.

These methods were applied to a study of the action of bradykinin in various species.

Bradykinin was given by infusion and by single injection. The effect of infusion was investigated in 13 rabbits. Doses ranged from 0.05 μg/kg/min to 2.0 μg/kg/min continued for 10 min. In all animals blood pressure fell initially by amounts proportional to the concentration. In all perfusions, however, whatever the concentration, the blood pressure drop was transient, the pressure returning to resting levels or near resting levels within 5 to 10 min.

Blood flow responses were variable. When vascular resistance was calculated as pressure/flow, however, the results were consistent in every experiment. Vascular resistance always fell with bradykinin, the initial fall being a function of the dose. In every experiment and at all dose levels, however, vascular resistance recovered during the infusion *pari-passu* with the recovery in blood pressure, to resting or near resting levels.

Changes in heat production were not observed during infusions with bradykinin.

The effect of 40 single injections was investigated in 11 rabbits. Doses given ranged from 0.05 μg to 20 μg/kg.

The effect on blood pressure was consistent. Blood pressure fell by an amount proportional to the dose.

The effect on blood flow was variable and not directly related solely to the dose.

The effect on vascular resistance, however, was consistent in all experiments (Figure 1). Small doses of bradykinin produced small changes in resistance, large doses produced reductions of resistance of up to 50%, the magnitude of the change being a function of the dose.

The effect of bradykinin on corrected temperature was also recorded in the above experiments. A typical result is shown in Figure 1. Small doses of bradykinin had no effect. Doses of 5 μg/kg or more produced marked increments in corrected temperature.

In order to confirm that these effects were, in fact, due to change in myocardial heat production, experiments were performed in which absolute temperature was recorded by means of fine gauge thermocouples from the myocardium, the aorta and the thoracic cavity near the heart. In these experiments the temperature of the myocardium was the same as, or slightly hotter than, that of the aortic blood, the temperature of the thoracic cavity being lower than either. Injections of bradykinin in doses of 5.0 μg/kg increased the differential (i.e. myocardial temperature rose more than aortic) by values ranging from 0.06 to 0.38°C (Figure 2).

Since the heart was surrounded by a medium cooler than itself it could only attain a temperature higher than that of the afferent blood by virtue of considerable local heat production. A further increase of myocardial temperature relative to the afferent blood can only be interpreted as direct evidence of increased local heat production.

In the rabbit, therefore, we have concluded that bradykinin has a 'threshold' effect on heat production, small

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