cyclic guanosine monophosphate, to the transformation system were examined to determine their ability to enhance transformation.

Materials and methods. The procedure for the preparation and isolation of a streptomycin-resistant mutant (STR) was similar to that of other investigators[6,7]. The actual procedure for the STR transformation experiment has been described elsewhere[2,3]. The minimal inhibitory concentration of nalidixic acid was determined according to the methods of GROOVE and RANDALL[8]. Competent cells were exposed to varying concentrations of this compound (100, 500 and 1000 μg) for 30 min during the latter segment of the log phase. From this point, the transformation was completed as described elsewhere[3]. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), at concentrations of 10 μg and 100 μg per ml, were added to the transformational system in the same manner as the nalidixic acid.

Results and discussion. The results of 3 independent studies showed a very slight reduction in the transformational frequency as compared with the controls when nalidixic acid at the 500 μg level was added to the log phase culture. No loss of viability at this concentration was observed. Greater concentrations demonstrated detrimental effects. These results indicate that DNA inhibition caused by nalidixic acid does not interfere with the transformation of *B. catarrhalis*, thus suggesting that nuclear replication may not be a prerequisite for this model. These results are similar to observations in other systems, such as *Neisseria meningitidis*[9], *Bacillus subtilis*[10], and *Streptococcus pneumoniae*[11]. ARCHER and LANDMAN[12] have shown that donor DNA can enter a competent cell regardless of the location of replicative points of the recipient DNA on the membrane. This would indicate that DNA can enter at any point on the membrane where receptors are located, and not just at points where DNA synthesis is occurring.

The exposure of competent cells to cAMP and cGMP prior to the addition of DNA did not alter in any way the transformational frequency in this model system. Inhibitors of energy metabolism have been shown to block DNA uptake in the pneumococci[13,14]; in *Hemophilus influenzae*[15]; in *B. subtilis*[16]; in *N. meningitidis*[9] and in *B. catarrhalis*[3]. It seems reasonable that if energy is required for DNA uptake, supplying a population of competent cells with a source of preformed energy molecules would be stimulatory to transformation. Although the role of these two chemicals in the cell is not completely understood, it appears that cAMP in particular may serve as an activator of synthesis of many catabolic enzymes[17]. WISE, POWERS and ALEXANDER[18] have found that cAMP added to exponential cultures of *H. influenzae* raises the transformability of cells as much as 10,000 fold after one generation time in growth medium. Either these energy precursors have no stimulatory effect on this model, or the cells do not possess a transport system for them. Another alternative is that the cells must actively engage in energy metabolism to achieve uptake. This is supported by the work of LACKS and GREENBERG[19] who have shown that an exogeneous source of ATP cannot substitute for sugar in the medium for DNA uptake in *St. pneumoniae*.

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Insulin Resistance and Related Electrical Activity of the Small Intestine

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Summary. Postprandial disruption of the migrating myoelectric complex is of longer duration in obese hyperinsulemic Zucker rats than in control rats. No postprandial disruption was seen in an insulin resistant dog. This gives further support to a major role for insulin in control of gut activity.

A cyclic recurring sequence of regular spiking activity (RSA) in which spike bursts are superimposed on all slow waves is characteristic of the small intestine in many species, e.g. rats or dogs fasted for 24 h[2]. Each phase of RSA is preceded by a period of irregular spiking activity (ISA) and followed by a quiescent phase. This cyclic pattern has been called the migrating myoelectric complex (MMC), because of its slow propagation along the small intestine. The MMC recurs at intervals of about 15 min in rats and 80–110 min in dogs[3]. The MMCs disappear after feeding being replaced by a postprandial

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pattern of continuous spiking activity characterized by randomly occurring spike bursts. This activity occurs throughout the night in rats fed ad libitum and for 7 to 8 h following one daily meal in dogs, even after vagotomy and/or splanchnicectomy.

The mechanisms controlling this electrical activity are less well understood. Gastrin release by food nutrients has been suggested as a possible mediator, but the effect of exogenous pentagastrin was short-lived in dogs[4]. In contrast, the injection of insulin secretagogues mimicked the postprandial pattern. The duration of postprandial hyperinsulinemia was also correlated with the period of MMC disruption, thus suggesting that endogenous insulin may be a controlling factor of intestinal motility[5].

The present study attempted to substantiate this hypothesis using Zucker obese rats (*fa/fa*), which are characterized by hyperinsulinemia and peripheral insulin resistance[6]. Additional observations were made on a dog which was hyperphagic (bulemy) and exhibited variable resistance to exogenous insulin injection.

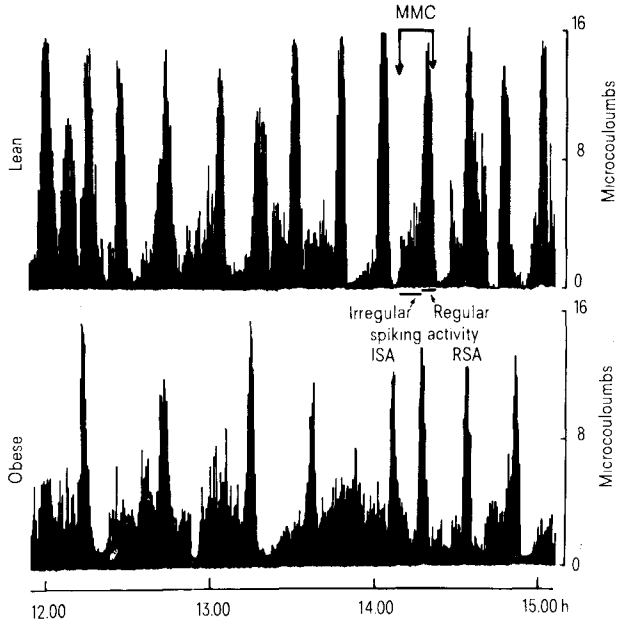

Fig. 1. Electrical spiking activity of the proximal jejunum (13 cm from the pylorus) integrated at 20-sec intervals in the rat. The number of MMC is about 3/h in the lean rat versus 1.7 in the obese rat. Maximum amplitude corresponds to the phase of RSA, preceded by that of ISA. The MMCs are separated by periods of relative auiescence.

Methods. 10 male Zucker rats (16 weeks of age), 5 obese (*fa/fa*) weighing about 500 g and 5 lean (*Fa-*) weighing about 300 g were housed singly in wire-bottomed cages and allowed lab chow and water ad libitum at night (18.00 to 08.00 h) over an experimental session of 6 weeks. Food was withheld during day-time but water was continuously available. Electrodes were implanted in the intestinal wall under ether anaesthesia[3]. 3 pairs of electrodes 2 mm apart were positioned at 5, 13 and 18 cm from the pylorus. The free ends of the electrodes were placed subcutaneously on the back of the neck. Starting 10 days after surgery, the electromyogram was registered with an EEG machine (Reega VIII, Alvar) for 10 consecutive h each day. The electrical activity was continuously plotted at 20-sec intervals using a double linear integrator circuit connected to a potentiometric recorder.

Among several routine preparations of mongrel dogs used for continuous recording of the myoelectrical activity of the small intestine, 1 animal (female, 6 months old, 17 kg) showed a consistent MMC pattern which was only briefly disrupted after a daily meal of 400 g of canned food. The plasma insulin level (IRI) in this animal was determined by radioimmunoassay[6] on jugular blood samples taken at 30-min intervals before and after feeding on 3 occasions. Results are expressed as the integrated response (Σ insulin, μU.min.ml^{-1}) = area subscribed by the insulin response curve during 180 min after feeding). The duration of disruption of the MMC pattern by the i.v. injection of insulin (3 IU/kg) following a 24-h fast was also determined in 3 instances. A control dog was subjected to the same protocol[7].

Results. Both lean and obese rats exhibited the MMC pattern from 08.00 to 18.00 h and the postprandial pattern previously described in the Wistar breed[2,3] from 18.00 to 08.00 h. As soon as food was withdrawn, the electrical spiking activity became regularly interspersed at 15-min intervals with periods of quiescence in the lean rats. In obese rats, the intervals between MMCs were generally longer and remained very irregular (Figure 1). The phases of RSA lasted about 4 min in both lean and obese rats, but the phases of ISA varied considerably in the obese rats, the mean duration being more than doubled. On occasion, a phase of ISA persisted over 30 min. The mean number of MMC per hour on the proximal part of the small intestine averaged 2.6 to 3.4 in the lean rats and only 1.2 to 1.6 in the obese rats (Table).

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Recurrence of the MMC at two electrode sites on the small intestine in 5 lean and 5 obese Zucker rats (mean values ± SD for 3 recordings from 08.00 to 18.00 per animal)

	Rats			
	Lean (*Fa*)		Obese (*fa/fa*)	
Electrode distance from the pylorus (cm)	5	18	5	18
MMC (per h)	2.6 ± 0.9	3.4 ± 1.1	1.2 ± 0.6[b]	1.6 ± 0.7[b]
Duration of RSA (min)	4.3 ± 0.6	4.0 ± 0.9	3.9 ± 0.3	3.9 ± 0.6
Intervals between MMC (min)	8.6 ± 3.9	8.4 ± 1.7	18.4 ± 7.7[b]	17.4 ± 7.1[b]
Plasma IRI[a] (μU/ml)	37.3 ± 6.3		270.7 ± 72.8	

[a] From STERN et al.[6]. [b] $P < 0.01$.

During the first 2 weeks of sampling and recordings, the insulin-resistant dog showed a very uniform recurrence of the MMC at regular intervals (90 ± 3 min). Exogenous insulin was followed by a postprandial pattern of less than 3 h vs. 6 h in the control and feeding disrupted the MMC for only 0.5 to 3 h. The plasma IRI level before (30.3 μU.ml^{-1}) and after (ΣIRI 8,190) feeding was higher than in the control dog (10.9 ± 8.1 μU.ml^{-1} and ΣIRI 1,042 ± 456. SEM). A decrease in the initial insulin resistance of the dog might be suspected since the last week of recording its natural bulemy slightly decreased and the Σ IRI value fell to 870. Despite a reduced food intake (300 vs. 400 g), the duration of the postprandial pattern was increased (Figure 2) and in the last week of time the MMC also recurred more irregularly during the interdigestive periods, resembling that of the control dog.

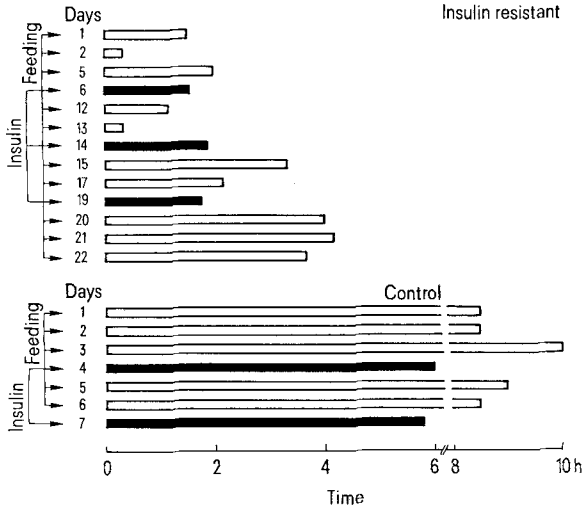

Fig. 2. Duration of the postprandial pattern of electrical activity after a daily meal (400 g) or i. v. injection of insulin (3 IU/kg) in an insulinresistant dog recorded over 22 days compared with a control dog over 7 days.

Discussion. A direct action of insulin on intestinal smooth muscle in vitro was described as early as 1932[8]. A low level of insulin may have a permissive role in vivo in the recurrence of the basic MMC pattern, the postprandial hyperinsulinemia being responsible for the disruption of the MMC. An imbalance between hyperinsulinemia and insulin peripheral resistance seems to exist in both genetically obese rats and the bulemic dog. A relatively greater increase in plasma IRI level than in intestinal insulin resistance would explain the irregular MMC pattern in obese rats during day-time. On the other hand, a higher insulin resistance as shown by the diminished response to exogenous insulin may explain the brevity of the disruption of the MMC pattern after feeding in the bulemic dog as well as the regularity of this pattern during the interdigestive periods.

Insulin may not be the only hormone regulating gastrointestinal electrical activity. Other intestinal hormones, such as enteroglucagon, motilin and gastric inhibitory polypeptide may be involved: recent observations of hyperplasia of gut endocrine cells in genetically obese mice suggest that changes in these hormones may also be significant in the Zucker rat[9]. However, the present results give further support to a major role of insulin in the control of gut electrical spiking activity.

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Ultradian and Other Rhythms in Human Respiration Rate

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Summary. Twelve male subjects had their respiration rate (RR) measured at 3 min intervals for 6 h. Although there were substantial individual differences, most subjects demonstrated a 90 ± 15 min rhythm of RR, with several subjects also showing 60 ± 10 min and 30 ± 3 min rhythms.

The phenomenon of REM cycling throughout sleep has produced the proposal[1] that there is a basic rest activity cycle (BRAC) which is a fundamental 90 min rhythm in sleep and wakefulness. Others[2,3] are less specific about such a rhythm and consider that there may be desynchronized ultradian rhythms (URs) in many body functions, with a duration of about 80–120 min. Whilst there are many equivocal findings with the presence of URs in wakefulness, perhaps a more definite UR is with orality[4,5] and gastric motility[6]. The equivocality may be due to such factors as; 1. insensitive measures, 2. URs do not exist in many body functions, 3. URs are vulnerable to intervening variables, e.g. light and darkness[3], and circadian rhythm modulation. Since the putative BRAC is associated with changes in levels of activity and wakefulness, measures of wakefulness may be particularly sensitive. There is some evidence[7] of a UR in waking EEG activity. It has been proposed[8] that respiration is a very sensitive measure of levels of wakefulness, with the proximity of the bulbo-pontine respiratory pacemaker

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