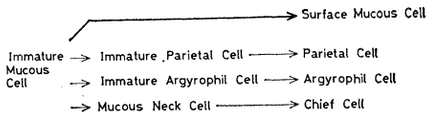

Fig. 3. Developmental relations of the specialized cells in the gastric glands.

logically observed in transition to this cell type (*9*). However, many electron microscopists have classified the cells as epithelial cells, because the cells abut on the basement membrane and are connected with the adjacent cells by the desmosomes (*10*). Our submicroscopic observation of immature argyrophil cells, as transitional cells, in the epithelial wall of the subcutaneous gastric grafts clearly demonstrated the epithelial nature of the cells. This was supported by the findings that rosette, acinar, or tubular structures in the human argentaffin cell tumor were formed by cells with microvilli (*11*) and that the neoplastic process in the stomach of the *Praomys* (*Mastomys*) *natalensis* began as a focal proliferation of argyrophil cells deep in the mucosa and infiltrated into the submucosa (*12*). Reported cases of human intestinal neoplasms with both carcinoid pattern and mucous secretion are also suggestive (*13*).

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Divergent Biological Effects of Adenosine and Dibutyryl Adenosine 3′,5′-Monophosphate on the Isolated Fat Cell

Abstract. *Adenosine 3′,5′-monophosphate stimulated production of carbon dioxide and lipid from glucose, whereas its dibutyryl derivative inhibited this conversion. Addition of the dibutyryl derivative to the isolated fat cell further stimulated lipolysis induced by adrenocorticotropic hormone, whereas addition of adenosine 3′,5′-monophosphate inhibited this lipolysis. Hence, measured by these two parameters, the biologic properties of adenosine 3′,5′-monophosphate and its dibutyryl derivative are distinctly different.*

Adenosine 3′,5′-monophosphate (cyclic AMP) has been indicated as a "second messenger" in multiple biologic systems. In particular, the reaction of multiple hormones has been shown to involve, at least in part, cyclic AMP and adenyl cyclase (*1*). Both cyclic AMP and its dibutyryl derivative (dibutyryl cyclic AMP) have been studied with regard to their ability to promote lipolysis (*2*). Although the biological effects of dibutyryl cyclic AMP were studied in fat (*3*) and muscle (*4*), the comparative effects of dibutyryl cyclic AMP and cyclic AMP have not been previously reported. This report presents new data on the effect of these two nucleotides in the isolated fat cell and compares their lipolytic and antilipolytic properties with those of glucose transport and oxidation. The insulin-like activity of the cyclic compounds was measured by incorporation of glucose, uniformly labeled with ^{14}C, into $^{14}CO_2$ and lipids in the isolated fat cell of the rat by the method of Gliemann (*5*) as modified by Kitabchi (*6*). As an index of lipolysis, the release of glycerol from the isolated fat cell was determined enzymatically by the method of Chernick (*7*).

Table 1. Effects of dibutyryl cyclic AMP and cyclic AMP on lipolysis in the presence and absence of ACTH.

Addition	Concentration per milliliter	Nanomoles of glycerol* released per 10^5 cell/1 hour
Base		7.5 ± 3.2
Dibutyryl cyclic AMP	1.0 μmole	299.1 ± 18.5
Cyclic AMP	2.5 μmole	31.4 ± 9.1
ACTH	0.2 μg	741.6 ± 7.3
ACTH + dibutyryl cyclic AMP	0.2 μg + 1 μmole	916.7 ± 57.3
ACTH + cyclic AMP	0.2 μg + 2.5 μmole	456.3 ± 21.4

* Condition of experiment is the same as in Fig. 1, except that the results are reported as nanomoles of glycerol released per 10^5 cells per 1 hour. The values are an average of three observations, ± standard error of the mean.

Figure 1, A and B, depicts the results of experiments in which the effect of varying concentrations of cyclic AMP and its dibutyryl derivative were tested on glucose oxidation and uptake. The dose-response curve of cyclic AMP on glucose conversion to CO_2 follows a pattern showing marked stimulation of this conversion at low concentrations of cyclic AMP, with more gradual stimulation at higher concentrations. In contrast, dibutyryl cyclic AMP does not act in the same way as cyclic AMP, but instead inhibits the conversion of glucose to CO_2 below the base line in a manner proportional to the concentration of dibutyryl cyclic AMP in the solution. Essentially similar results were obtained when the conversion of glucose carbon into lipids was measured, that is, cyclic AMP stimulated, whereas dibutyryl cyclic AMP inhibited, lipogenesis from glucose.

The lipolytic effects of cyclic and dibutyryl cyclic AMP were measured at both high and low concentrations of nucleotide and compared to high and low concentrations of insulin. The data in Table 1 show that both dibutyryl cyclic and cyclic AMP promote endogenous lipolysis and that dibutyryl cyclic AMP potentiates the lipolytic effect of adrenocorticotropic hormone (ACTH), but cyclic AMP inhibits lipolysis induced by ACTH. The antilipolytic property of cyclic AMP on ACTH-induced lipolysis has not hitherto been reported. To study this mechanism of the two

Table 2. Effect of insulin on lipolysis induced by cyclic AMP and dibutyryl cyclic AMP. Values are means ± standard error of the mean; n, number of observations per datum.

Insulin conc. (molar)	Nanomoles of glycerol released per 10^5 cells per 1 hour*				
	Control ($n = 10$)	Cyclic AMP		Dibutyryl cyclic AMP	
		2.5 mM ($n = 6$)	5.0 mM ($n = 5$)	0.5 mM ($n = 8$)	1.0 mM ($n = 8$)
0	13.2 ± 1.5	27.6 ± 3.7	39.4 ± 2.8	48.6 ± 7.3	147.5 ± 16.1
1.4×10^{-11}	20.1 ± 3.4	4.2 ± 2.4	26.5 ± 6.6	28.3 ± 2.6	112.0 ± 13.2
1.4×10^{-10}	26.2 ± 3.2	8.8 ± 7.3	41.0 ± 5.4	26.2 ± 3.6	118.9 ± 16.0
6.6×10^{-9}	39.1 ± 6.0	0.8 ± 0.2	33.5 ± 7.2	74.2 ± 4.0	263.7 ± 10.5

* The condition of experiment is the same as in Table 1.

nucleotides further, the effect of low and high concentrations of insulin was tested. At low concentrations of cyclic AMP, low concentrations of insulin exert an antilipolytic effect (see Table 2). However, this effect, in most cases, is nullified at higher concentrations of cyclic and dibutyryl cyclic AMP. The endogenous lipolytic effect of both nucleotides was markedly reduced by 2 μunit ($1.4 \times 10^{-11} M$) of insulin, but not at high concentrations of insulin. This suggests a competitive mechanism of inhibition between insulin and both forms of cyclic AMP. Hepp *et al.* (*2*) reported that insulin had no effect on lipolysis induced by cyclic and dibutyryl cyclic AMP, but that their measurements were made only at high concentrations of insulin.

It has previously been assumed that the increased potency of dibutyryl cyclic AMP over cyclic AMP may be due to its more nonpolar nature, which permits easier penetration of the cell membrane in the biological system. The data presented here suggest that other explanations, in addition to solubility, must be offered for the divergent action of these two nucleotides, since the more nonpolar analog of the two cyclic nucleotides, dibutyryl cyclic AMP, showed no stimulatory effect on glucose oxidation, whereas the presumed more polar analog, cyclic AMP, showed significant stimulation of glucose oxidation and lipogenesis. The question may now be raised as to the nature and structure of the "second messengers" in biological systems. Apparently, profound differences are introduced by the addition of the two butyrate moieties on the cyclic AMP molecule. These data, furthermore, serve to emphasize the caution that needs to be exercised in assigning biological roles to derivatives of cyclic nucleotides that do not in fact possess the same structure.

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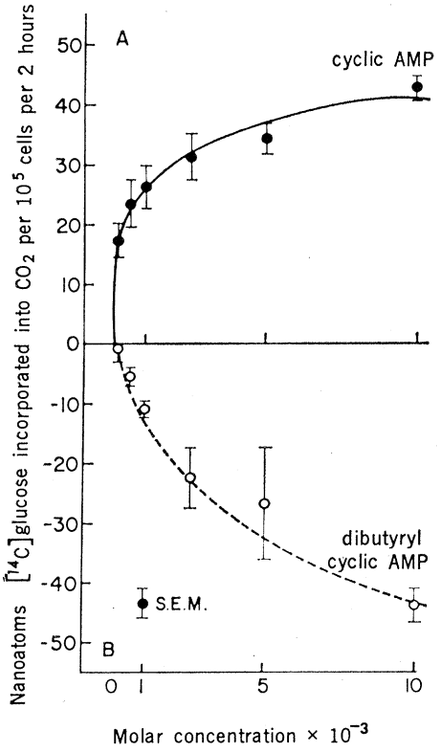

Fig. 1. Dose response curves for cyclic AMP (A) and dibutyryl AMP (B) as measured by glucose uptake and oxidation. The results are reported as nanoatoms of $^{14}CO_2$ released per 100,000 cells per 2 hours above or below the base line. The incubation system consists of 100,000 fat cells, 0.5 mM glucose in a Krebs-Ringer and bicarbonate buffer with 4 percent albumin (pH 7.4) in a total volume of 2 ml. Incubation was carried out under an atmosphere of 95 percent O_2 and 5 percent CO_2 at 37°C in the presence or absence of various concentrations of cyclic AMP or dibutyryl cyclic AMP. Each point is an average of five observations.

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Allopurinol: Alteration in Pyrimidine Metabolism in Man

Abstract. *In addition to its well-established inhibitory effect on uric acid synthesis, allopurinol appears to alter substantially pyrimidine metabolism, as evidenced by a striking increase in the urinary excretion of orotidine and orotic acid. Allopurinol ribonucleotide and xanthosine 5′-monophosphate are potent inhibitors of human erythrocyte orotidylic decarboxylase and provide a possible mechanism for this effect.*

Allopurinol [4-hydroxypyrazolo(3,4-*d*)pyrimidine] is widely used in the treatment of hyperuricemia and gout. This agent, an analog of hypoxanthine, is a potent inhibitor of xanthine oxidase, which catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid (*1*). Accordingly, its administration in man leads to a prompt decrease in the formation of uric acid and an increase in the excretion of hypoxanthine and xanthine (*2*). In the present study, we demonstrate that the administration of allopurinol and its major metabolic product, oxipurinol, also produces a substantial inhibition of de novo pyrimidine biosynthesis.

The urinary excretion of purines and pyrimidines in six patients with gout, before and during allopurinol therapy, was assessed with an ultraviolet analyzer (*3*). With the use of this instrument, low molecular weight constituents in urine are separated by automated high-resolution, high-pressure, anion-exchange chromatography and those substrates exhibiting absorbance in the ultraviolet spectrum are detected with a