Table II—Effect of *N*-Chloroacetyl Derivatives of *para*-Substituted Phenylalanines on the Growth of *L. casei*[a]

Compound	Concentration Equivalent at 1 mg/ml, m*M*	Inhibition[b], % 0.1 mg/ml[c]	0.5 mg/ml[c]	1.0 mg/ml[c]
N-Chloroacetyl-*p*-chloro-DL-phenylalanine	3.62	5	19	42
N-Chloroacetyl-*p*-nitro-DL-phenylalanine	3.49	3	10	18
N^{a},N^{p}-Di(chloroacetyl)-*p*-amino-DL-phenylalanine	3.00	6	13	21
N-Chloroacetyl-*O*-methyl-L-tyrosine	3.68	4	11	20
N-Chloroacetyl-*p*-bromo-DL-phenylalanine	3.12	2	25	56
N-Chloroacetyl-*p*-iodo-DL-phenylalanine	2.72	+3	35	54

[a] For details of assay procedure, see Refs. 1 and 2. [b] Turbidity readings of the inoculated control tubes (containing no test compounds) were 188–196. [c] Final concentration in the assay system.

crystallization. Since widely different inhibitory activities were observed, contaminants producing inhibition would have had to be present in the original compounds and retained during the preparative and purification procedures. This is clearly not the case since compounds that were not chloroacetylated did not inhibit. Therefore, it seems reasonable that the inhibitory activities are intrinsic properties of the newly synthesized compounds and are related principally to the chloroacetylation of the amino group and, secondarily, to the introduction of substituent groups into the aromatic ring of the amino acid.

Table III—Comparison of the Effect of Equimolar Concentrations of *N*-Chloroacetyl Derivatives of *para*-Substituted Phenylalanines on the Growth of *L. casei*[a]

Compound	Inhibition[b], %
N-Chloroacetyl-*p*-chloro-DL-phenylalanine	48
N-Chloroacetyl-*p*-nitro-DL-phenylalanine	19
N^{a},N^{p}-Di(chloroacetyl)-*p*-amino-DL-phenylalanine	22
N-Chloroacetyl-*O*-methyl-L-tyrosine	20
N-Chloroacetyl-DL-phenylalanine	20
N-Chloroacetyl-*p*-bromo-DL-phenylalanine	86
N-Chloroacetyl-*p*-iodo-DL-phenylalanine	93
p-Bromo-DL-phenylalanine[c]	+3
p-Chloro-DL-phenylalanine[c]	0
p-Iodo-DL-phenylalanine[c]	0

[a] Maximum growth in inoculated control tubes (containing no test compound) was 186–196 Klett units. [b] Concentration was 4.47 μmoles/ml and was the final concentration of the assay system. [c] Free amino acid.

In studies of this nature, where empirical relationships of inhibitory capabilities are sought, there is little information regarding the mechanism of action. To study the mechanism of action, more sophisticated experiments are required.

The activity of the *N*-benzoyl-*p*-bromo and *N*-benzoyl-*p*-iodophenylalanine is being studied and compared with the corresponding *N*-chloroacetyl compounds.

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COMMUNICATIONS

Nasal Absorption of Natural Contraceptive Steroids in Rats—Progesterone Absorption

Keyphrases □ Progesterone—nasal absorption compared with that following intravenous and intraduodenal administration, rats □ Absorption, nasal—progesterone, compared with absorption following intravenous and intraduodenal administration, rats □ Contraceptives, natural—progesterone, nasal absorption compared with that following intravenous and intraduodenal administration, rats □ TLC—identification of unchanged progesterone following nasal administration to rats, compared with intravenous and intraduodenal administration

To the Editor:

Contraceptive natural steroids such as progesterone and estradiol are ineffective when given orally due to extensive metabolism in the GI tract during absorption and first-pass metabolism (1, 2). Thus, highly potent and potentially harmful synthetic steroids are currently being used in oral dosage forms.

To enhance progesterone bioavailability from nonparenteral routes, the nasal route was examined. Previous studies showed that propranolol is absorbed efficiently from the nasal mucosa of rats and dogs (3, 4). Sprague–Dawley male rats, 300 g, were anesthetized with pentobarbital sodium (50 mg/kg). For each dose and for each administration route, four to six rats were used.

For nasal administration, three doses of 50, 100, and 150 μg of [4-^{14}C]progesterone (8 μCi) in 0.1 ml of 1% polysorbate 80–saline solution were administered to the nasal cavity of each rat by a micropipet according to the procedure described previously (3). For intravenous administration, the same doses were injected through the femoral vein. For intraduodenal administration, the abdomen was opened by a midline incision, and the 50-μg dose in 0.1 ml of 1% polysorbate 80–saline solution was injected directly through the duodenum.

After administration, 0.2 ml of blood was sampled periodically from the femoral aorta. The blood sample was

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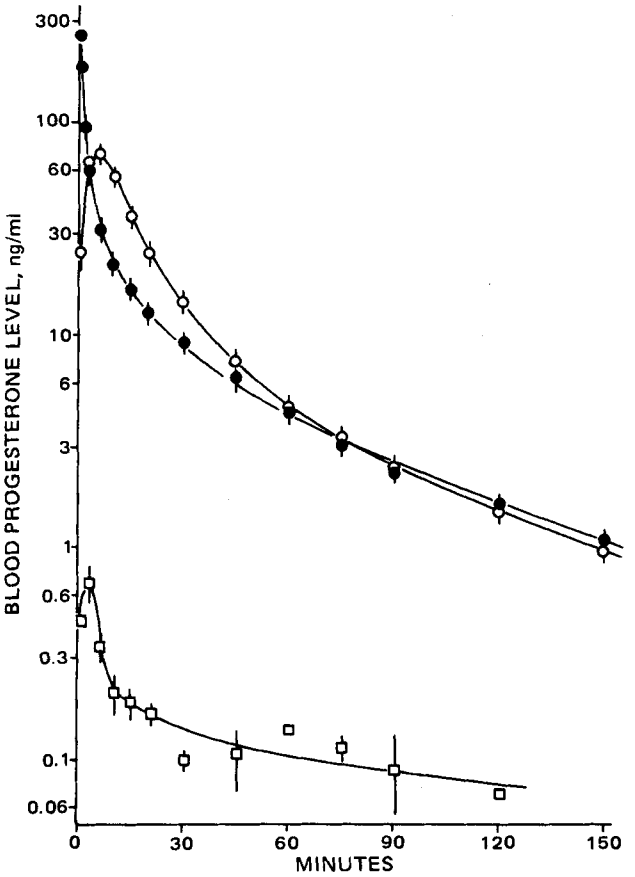

Figure 1—*Mean blood progesterone levels after nasal (○), intravenous (●), and intraduodenal (□) administration of 50 μg of progesterone. The lines were drawn through the points, and the vertical bars represent standard error.*

shaken with 5 ml of ether, and the ether layer was evaporated to dryness. The residue then was dissolved in 50 μl of toluene, and 40 μl was spotted on TLC plates and developed using toluene–ethanol (9:1 v/v). The spot that corresponded to unchanged progesterone then was scraped off the plate, and the powder was suspended in scintillation cocktail for a radioactivity count. The developing solvent system separated the unchanged progesterone from its metabolites.

Figure 1 shows the mean blood progesterone levels for the three administration routes at the 50-μg dose. The

Table I—Area under the Curves after Intravenous, Nasal, and Intraduodenal Administration of Progesterone in Rats

Dose, μg/rat	AUC_0^∞, (ng min)/ml			Nasal	Intraduodenal
	Intravenous	Nasal	Intraduodenal	Intravenous	Intravenous
50	1612.2[a] ±80.8	1659.0 ±109.2	19.0 ±4.6	1.029	0.012
100	3520.0 ±491.0	3599.0 ±621.4	—	1.022	—
150	4480.2 ±466.4	4798.9 ±188.5	—	1.071	—

[a] Mean ± *SE* (n = 4–6).

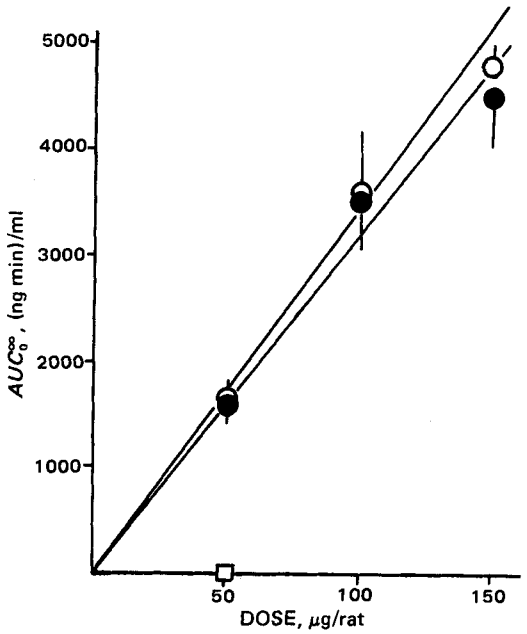

Figure 2—*Relationship between dose and* AUC *after nasal (○) and intravenous (●) administration of progesterone. The square (□) represents intraduodenal administration. The vertical bars represent standard error.*

blood drug levels after nasal administration increased rapidly and attained the peak level within 6 min, whereas the intraduodenal administration resulted in considerably lower blood levels.

Table I and Fig. 2 summarize the area under the blood drug level curve (*AUC*) for the three administration routes at various doses. The *AUC* was directly proportional to the dose administered nasally and intravenously. The nasal bioavailability calculated from the ratio of the *AUC* [(nasal/intravenous) × 100] was 100% at the different doses; the intraduodenal bioavailability was only 1.2% that of the intravenous bioavailability at the dose studied.

These results indicate that the natural contraceptive steroid, progesterone, is absorbed rapidly from the nasal mucosa into systemic blood without first-pass metabolism and that nasal administration of progesterone is superior to the intraduodenal route.

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