Since many antiarrhythmic agents seem to possess some degree of local anesthetic action, those compounds, namely, Id, IIb, IIIa, and IIIb, were tested for local anesthetic activity. Table VI is the summary of the results of the testing. Due to the limited number of tests, the data in this table were not analyzed statistically to determine if the average percent anesthesia of the compounds was significantly higher than that of procaine. Therefore, the results should be treated qualitatively rather than quantitatively. It is not surprising that Compounds IIb, IIIa, and IIIb showed local anesthetic activity, because in addition to structural similarity these compounds had a pKa value very close to that of procaine.

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In Vivo Evaluation of Absorption and Excretion of Pentylenetetrazol-10-^{14}C from Sustained-Release and Nonsustained-Release Tablets

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Abstract □ Sustained-release and nonsustained-release tablets containing pentylenetetrazol-10-^{14}C were administered orally to human volunteers. The levels of the drug and/or its labeled metabolites in the plasma and urine were determined by liquid scintillation counting. These data showed that the sustained-release tablets provided a consistent plasma level of ^{14}C for about 12 hr. and that the drug and/or its labeled metabolites were excreted in the urine at a fairly constant rate during this period. The nonsustained-release tablets given in divided doses resulted in three separate peak plasma-^{14}C levels and a urinary excretion pattern similar to that of the sustained-release tablet. A single dose of the nonsustained-release tablet was followed by a peak plasma-^{14}C level, which decreased during the 12 hr. after administration, and by a fairly constant rate of urinary excretion of ^{14}C during this period.

Keyphrases □ Pentylenetetrazol-10-^{14}C—absorption, excretion □ Tablets, sustained-, nonsustained-release—pentylenetetrazol-10-^{14}C □ Absorption, excretion—pentylenetetrazol-10-^{14}C from sustained-, nonsustained-release tablets □ Scintillometry—analysis

Sustained-release[1] and nonsustained-release tablets containing pentylenetetrazol and niacin in common therapeutic dosages have been evaluated for their *in vivo* performance in humans by following niacin–plasma levels (1). This evaluation was accomplished by using ^{14}C-labeled niacin in the tablets and determining the plasma and urine levels of niacin-^{14}C and/or its labeled metabolites subsequent to oral administration of the tablets. The results of this study showed that after ingestion of sustained-release tablets, the plasma level of niacin-^{14}C and/or its labeled metabolites was sustained for a 12-hr. period. In contrast, three doses of nonsustained-release tablets, administered at 4-hr. intervals, resulted in three peak plasma levels. The drug excretion patterns observed after both dosage regimens were similar.

Because of the various chemical, pharmacological, and metabolic differences between niacin and pentylenetetrazol, different absorption and excretion patterns for the two drugs were expected. The present paper reports a study of the absorption and excretion patterns characteristic of pentylenetetrazol administered orally, combined with niacin, in both sustained-release and nonsustained-release dosage forms. Pentylenetetrazol-10-^{14}C was used in this study to permit determination of these patterns by radiotracer techniques similar to those originally reported by Rosen and Swintosky (2) for following the appearance of a drug in human plasma and urine.

[1] Geroniazol TT, Philips Roxane Laboratories, Columbus, Ohio.

Table I—*In Vitro* Determination of Cumulative Pentylenetetrazol and Niacin Release from Sustained-Release Tablets

Time, hr.	Mean % Pentylenetetrazol Released ± *SD* — Chemical Assay	Mean % Pentylenetetrazol Released ± *SD* — ^{14}C Assay	Mean % Niacin Released ± *SD*
1[a]	40.5 ± 0.9[b]	41.8 ± 0.6[b]	30.8 ± 0.2[c]
4[d]	69.9 ± 1.9[e]	73.8 ± 1.0[e]	58.0 ± 2.0[f]
8[d]	89.8 ± 0.3[g]	92.9 ± 0.7[g]	77.8 ± 1.0[h]

[a] Mean of six tablets; simulated gastric solution test fluid. [b] Established limit for commercial forms is 40.0 ± 3.0%. [c] Established limit for commercial forms is 30.0 ± 5.0%. [d] Mean of three tablets; simulated intestinal solution test fluid. [e] Established limit for commercial forms is 73.0 ± 5.0%. [f] Established limit for commercial forms is 57.5 ± 7.5%. [g] Established limit for commercial forms is 92.5 ± 7.5%. [h] Established limit for commercial forms is 82.5 ± 7.5%.

EXPERIMENTAL

Radioactive Pentylenetetrazol—Pentylenetetrazol-10-^{14}C with a specific activity of 17.8 μc./mg., as synthesized[2] by Stiver, and with radiochemical purity established by TLC (3) was diluted (4) with nonradioactive pentylenetetrazol NF XII. Three separate dilutions of pentylenetetrazol-^{14}C were prepared, and the resulting specific activities were 23.4 μc./300 mg., 18.5 μc./100 mg., and 9.3 μc./100 mg. Each dilution was prepared by dissolving pentylenetetrazol-10-^{14}C and pentylenetetrazol NF XII in methanol (99.85%) with stirring. The methanol was evaporated over a steam bath. The pentylenetetrazol-^{14}C thus obtained was then cooled to room temperature and dried in a vacuum desiccator at 0.05 mm. at room temperature for 6 hr.

Radioactive Tablets—Three different compressed tablet formulations were manufactured from the pentylenetetrazol-^{14}C dilutions as follows.

Formula A—Sustained-release tablets, of the insoluble matrix type, from which the active ingredients are slowly leached; identical to commercial forms,[1] with the exception of the use of pentylenetetrazol-^{14}C. These tablets contained pentylenetetrazol-^{14}C, 300 mg. (equivalent to 23.4 μc. of ^{14}C); niacin, 150 mg.; fatty substances; and inert excipients.

Formula B—Nonsustained-release tablets containing pentylenetetrazol-^{14}C, 100 mg. (equivalent to 18.5 μc. of ^{14}C); niacin, 50 mg.; and inert excipients.

Formula C—Nonsustained-release tablets containing pentylenetetrazol-^{14}C, 100 mg. (equivalent to 9.3 μc. of ^{14}C); niacin, 50 mg.; and inert excipients.

Quality Control—Tablets were selected at random from all three tablet formulations; they were subjected to routine quality control tests to establish the conformance of the pentylenetetrazol-^{14}C-containing sustained-release tablets to the commercial forms and to determine that the physical and chemical characteristics of the nonsustained-release tablets were satisfactory with reference to commercially available tablets of similar composition. Tablets were tested for pentylenetetrazol content, niacin content, weight, thickness, and hardness. The disintegration time of the nonsustained-release tablets was determined by the USP Tablet Disintegration Test, and the *in vitro* release rate was determined for the sustained-release tablets.

***In Vitro* Release Rate Tests**—Before the sustained-release tablets were administered to human subjects, the *in vitro* release rates of pentylenetetrazol and niacin were determined to establish conformance of the radioactive tablets to commercial forms. The USP Tablet Disintegration Test Apparatus (5) was used to determine the *in vitro* release rates as follows. Six tablets were chosen at random and tested individually by placing one tablet in one of the six tubes of the basket-assembly, which was then immersed in 600 ml. of simulated gastric fluid T.S. (6) at 37 ± 1°. After operation of the apparatus for 1 hr., the basket was removed, rinsed, and transferred immediately to 600 ml. of simulated intestinal fluid T.S. (7) at 37 ± 1° in which the apparatus was operated for 7 hr.

At the end of the 1st hour, samples of the gastric test fluid were assayed for pentylenetetrazol by both the liquid scintillation counting technique and by gravimetric analysis. In the latter procedure, an aliquot of the test fluid was saturated with ammonium sulfate and the pentylenetetrazol quantitatively extracted with carbon tetrachloride. After evaporation of the solvent, the residue was dissolved in a small volume of ether and evaporated to dryness; the process then was repeated. The weight of the residue was determined after drying in a vacuum at room temperature to constant weight. The niacin was quantitated by UV spectrophotometry with a correction for the background absorbance due to the gastric test fluid. Samples of the intestinal test fluid were withdrawn at 4 and 8 hr. after the start of the test and were assayed similarly after acidification of the release solutions.

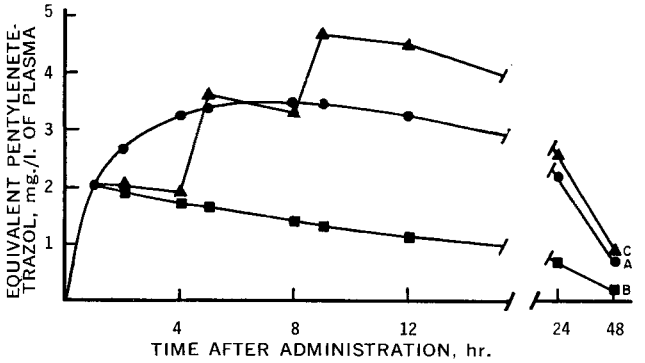

Figure 1—*Average plasma levels of equivalent pentylenetetrazol following oral administration of pentylenetetrazol-^{14}C tablets. Group A: One sustained-release tablet. Group B: One nonsustained-release tablet. Group C: One nonsustained-release tablet at 0, 4, and 8 hr. For clarity, standard deviations are not shown on the curves but are given in Table II.*

***In Vivo* Protocol**—Twelve healthy adult human volunteers, determined by medical history and physical examinations to be free of any disorders associated with abnormal absorption or excretion patterns, were used in this study. The subjects were all Caucasian males, ranging in age from 25 to 34 yr. and weighing between 72.3 and 102.8 kg. Plasma and urine samples were obtained from all subjects before the experiment began for later use in background correction of sample assays. All subjects fasted for 12 hr. prior to the experiment and for 5 hr. after it began.

The 12 volunteers were assigned experimental subject numbers at random. Each of four subjects (Group A: Subjects 1, 2, 3, and 4) was given one tablet of Formula A, the sustained-release dosage form. Each of four other subjects (Group B: Subjects 5, 6, 7, and 8) was given one tablet of Formula B, a nonsustained-release tablet. Each of four additional subjects (Group C: Subjects 9, 10, 11, and 12) was given one tablet of Formula C, a nonsustained-release tablet, at time zero and again at 4 and 8 hr. after time zero. All tablets were ingested with water.

Ten-milliliter blood samples were withdrawn from all subjects at 1, 2, 4, 5, 8, 9, 12, 24, and 48 hr. after time zero. All blood samples were treated with 20 mg. of disodium EDTA, and the plasma was immediately separated by centrifugation and frozen until assayed. Total urinary collections were made for all subjects during the following intervals after time zero: 0–3, 3–6, 6–9, 9–12, 12–24, 24–36, 36–48, and 48–72 hr. The urine was frozen until analyzed.

Assay of ^{14}C—Liquid scintillation counting techniques were employed to determine the quantity of ^{14}C in each plasma and urine sample. In a preliminary experiment, replicate plasma samples were prepared for counting by three different methods, using Insta-Gel emulsifier,[3] hyamine hydroxide[4] solution, and perchloric acid. All three methods gave satisfactory results, but the Insta-Gel emulsifier system was determined most suitable on the basis of its simplicity and low quenching characteristics (counting efficiencies of approximately 80% were obtained).

Remaining plasma samples were prepared for counting as follows. Exactly 1 ml. of plasma was slowly added to a counting vial containing 10 ml. of emulsifier (Insta-Gel). The vial was tightly capped and allowed to remain at room temperature for 20 hr., with

[2] Synthesis conducted at the Bionucleonics and Medicinal Chemistry Departments, Purdue University, Lafayette, Ind.

[3] Packard Instrument Co., Inc., Downers Grove, Ill.

[4] *p*-(Diisobutyl-cresoxyethoxy ethyl)dimethylbenzylammonium hydroxide.

Table II—Plasma Levels of Equivalent Pentylenetetrazol following Oral Administration of Pentylenetetrazol-^{14}C Tablets

Time after Administration, hr.	Mean[a] Equivalent Plasma Pentylenetetrazol,[b] mg./l. ± *SD*		
	Group A[c]	Group B[d]	Group C[e]
1	2.1 ± 0.3	2.1 ± 0.3	2.1 ± 0.2
2	2.7 ± 0.3	2.0 ± 0.2	2.0 ± 0.2
4	3.2 ± 0.3	1.7 ± 0.1	1.8 ± 0.2
5	3.4 ± 0.3	1.7 ± 0.1	3.6 ± 0.9
8	3.5 ± 0.2	1.4 ± 0.0	3.3 ± 0.4
9	3.5 ± 0.2	1.3 ± 0.1	4.7 ± 0.5
12	3.2 ± 0.3	1.1 ± 0.1	4.5 ± 0.5
24	2.2 ± 0.4	0.7 ± 0.1	2.7 ± 0.6
48	0.7 ± 0.1	0.2 ± 0.1	0.9 ± 0.4

[a] Mean of four subjects. [b] Any ^{14}C-labeled metabolites have been equated to the administered pentylenetetrazol-^{14}C. [c] Group A: One sustained-release tablet containing 300 mg. of pentylenetetrazol-^{14}C. [d] Group B: One nonsustained-release tablet containing 100 mg. of pentylenetetrazol-^{14}C. [e] Group C: One nonsustained-release tablet containing 100 mg. of pentylenetetrazol-^{14}C at 0, 4, and 8 hr.

occasional shaking. Upon cooling to 4°, a viscous one-phase system was obtained.

Urine samples were prepared for counting by adding 1.0-ml. aliquots to 15 ml. of a scintillation solution containing 2,5-diphenyloxazole (PPO), 10.0 g.; naphthalene, 80.0 g.; *p*-xylene, 143 ml.; *p*-dioxane, 429 ml., and a sufficient quantity of 2-ethoxyethanol to make 1 l.

All samples were cooled to 4° and were counted at that temperature in a Packard Tri-Carb liquid scintillation spectrometer equipped with bialkali photomultiplier tubes. The discriminators were set at 50 and 900, and the gain was adjusted to optimize the counting rate. All samples were counted for a length of time sufficient to assure counting errors less than 5% (at the 95% confidence level) in all cases and less than 1% for the majority of the samples.

All sample count rates were corrected for background and converted to absolute count rates by the internal standardization method of quench correction. The results of the sample assays are expressed in terms of "equivalent pentylenetetrazol," thus equating any ^{14}C-labeled metabolites to the administered pentylenetetrazol-^{14}C, and assuming that the specific activities of all labeled compounds present in the urine and plasma are identical to the specific activity of the administered pentylenetetrazol-^{14}C.

RESULTS AND DISCUSSION

Tablet Assays—The *in vitro* release rate data for the sustained-release tablets (Formula A) are given in Table I. These data indicate that the radioactive sustained-release tablets met the specifications of the corresponding commercial form.

The data for quality control tests for total pentylenetetrazol, total niacin, weight, thickness, hardness, and disintegration time are not summarized in this paper but showed that all tablets tested conformed to corresponding commercially available forms.

Plasma Data—The average plasma levels of equivalent pentylenetetrazol are plotted for each test group in Fig. 1. This graph shows that the plasma levels of the parent compound and/or its labeled metabolites were identical (±0.01 mg./l.) for all three groups 1 hr. after drug administration. Plasma concentrations of equivalent pentylenetetrazol gradually rose during the 1–4-hr. period after administration of the sustained-release tablet and then remained constant (3.2–3.5 mg./l.) until about the 12th hour. However, during the 1–4-hr. period following administration of the nonsustained-release tablet, plasma-^{14}C levels gradually decreased. Typical rises and falls in plasma levels of equivalent pentylenetetrazol were observed following the repeated administration of the nonsustained-release tablet. The plasma level of equivalent pentylenetetrazol decreased continually after the peak seen 1 hr. after single-dose administration of the nonsustained-release tablet.

Table II gives the mean plasma levels of equivalent pentylenetetrazol and the standard deviations for all three groups at the various times studied. Student *t* values (8) were determined to compare the mean plasma levels of ^{14}C of the different groups at various times. At the 99% confidence level (p = 0.01), there were no statistically significant differences between the mean plasma levels of any

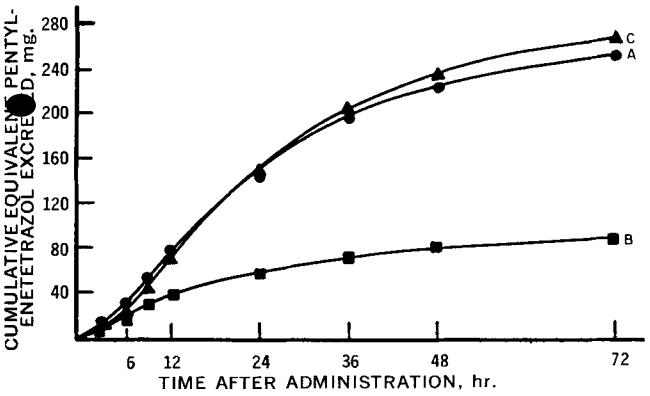

Figure 2—*Cumulative average urinary excretion of equivalent pentylenetetrazol following oral administration of pentylenetetrazol-^{14}C tablets. Group A: One sustained-release tablet. Group B: One nonsustained-release tablet. Group C: One nonsustained-release tablet at 0, 4, and 8 hr. For clarity, standard deviations are not shown on the curves but are given in Table III for the noncumulative excretion data. (The value of Group C, 24–36-hr. collection, includes an estimate of the amount of pentylenetetrazol present in a quantity of urine which was voided but not collected for analysis. (One subject forgot to collect one urine sample voided during this interval.)*

two groups 1 hr. after drug administration. At all times after 1 hr., the mean plasma levels of Groups A and B (the sustained-release tablet group and the single-dose, nonsustained-release tablet group) were significantly different. This indicates that the sustained-release tablet was still releasing pentylenetetrazol after the 1st hour, whereas the peak plasma level resulting from dosage with one nonsustained-release tablet occurred prior to or approximately at 1 hr.

Statistically significant differences were found between Groups A and C (the sustained-release tablet group and the group that received three divided doses of a nonsustained-release tablet) only at 2, 4, 9, and 12 hr. These results suggest that the sustained-release tablet released about one-third of the pentylenetetrazol rapidly and that the remainder was smoothly and continuously released.

As expected, there was no statistically significant difference between Groups B and C (the groups receiving nonsustained-release tablets in single doses and in three divided doses) at 1, 2, or 4 hr. From 5 hr. on, differences between these two groups were significant.

Urine Data—Urinary excretion of equivalent pentylenetetrazol proceeded at a nearly constant rate for approximately 36 hr. after administration of the sustained-release tablet and then gradually decreased (Fig. 2). A similar excretion pattern was shown by those subjects receiving three nonsustained-release tablets at 4-hr. intervals. A constant rate of urinary excretion of equivalent pentylenetetrazol was evident for approximately 24 hr. following single oral

Table III—Urinary Excretion of Equivalent Pentylenetetrazol following Oral Administration of Pentylenetetrazol-^{14}C Tablets

Time after Administration, hr.	Mean[a] Equivalent Pentylenetetrazol[b] Excreted, mg. ± *SD*		
	Group A[c]	Group B[d]	Group C[e]
0–3	12.3 ± 4.4	9.3 ± 3.9	8.8 ± 3.0
3–6	19.5 ± 2.7	9.3 ± 3.4	13.9 ± 2.8
6–9	23.0 ± 4.9	10.8 ± 1.5	19.7 ± 7.2
9–12	24.7 ± 4.1	8.2 ± 1.3	26.4 ± 7.7
12–24	65.9 ± 5.2	21.5 ± 0.4	79.7 ± 10.6
24–36	51.8 ± 11.9	12.8[f] ± 4.9	55.3 ± 11.5
36–48	27.2 ± 5.5	7.9 ± 2.0	31.2 ± 7.0
48–72	23.5 ± 4.8	7.6 ± 1.6	30.6 ± 10.6

[a] Mean of four subjects. [b] Any ^{14}C-labeled metabolites have been equated to the administered pentylenetetrazol-^{14}C. [c] Group A: One sustained-release tablet containing 300 mg. of pentylenetetrazol-^{14}C. [d] Group B: One nonsustained-release tablet containing 100 mg. of pentylenetetrazol-^{14}C. [e] Group C: One nonsustained-release tablet containing 100 mg. of pentylenetetrazol-^{14}C at 0, 4, and 8 hr. [f] This value includes an estimate of the amount of pentylenetetrazol present in a quantity of urine which was voided but not collected for analysis. (Subject forgot to collect one urine sample voided during this interval.)

administration of the nonsustained-release tablet, with the rate decreasing after the 24-hr. point.

The mean equivalent pentylenetetrazol excretion values and the standard deviations for the three groups are given in Table III. Student t values (8) were calculated to compare the mean ^{14}C excretion values of the different groups at various times. Statistically significant ($p = 0.01$) differences were seen between Groups A and B at all collection intervals after the first (0–3 hr.).

No significant differences between Groups A and C were present at any of the collection intervals. These results indicate that urinary excretion of 300 mg. of pentylenetetrazol proceeds at approximately the same rate whether the dose is administered in one sustained-release tablet or divided and administered in three doses at 4-hr. intervals. These results also indicate that the same fraction of pentylenetetrazol was absorbed from the sustained-release tablets as from the nonsustained-release tablets.

There were no significant differences between Groups B and C until the fourth collection (9–12 hr.). Mean excretion values for these two groups were significantly different in all of the last five urine collections.

SUMMARY

Sustained-release and nonsustained-release tablets containing pentylenetetrazol-10-^{14}C were administered to human subjects. The resulting plasma and urine concentrations of equivalent pentylenetetrazol were determined by liquid scintillation counting techniques. Subjects receiving the sustained-release tablets exhibited smoothly sustained plasma levels of equivalent pentylenetetrazol for a period of about 12 hr. and a nearly linear urinary excretion rate of ^{14}C during a period of 36 hr. Subjects receiving three doses of nonsustained-release tablets at 4-hr. intervals exhibited typical rises and falls in plasma ^{14}C levels and an excretion pattern similar to that of the subjects receiving the sustained-release tablets. Subjects receiving a single dose of a nonsustained-release tablet showed one peak plasma ^{14}C level which then decreased continuously. A fairly constant rate of urinary ^{14}C excretion was evident for 24 hr. The results of this study showed that the sustained-release tablet produced absorption and excretion patterns similar to those obtained following three doses of the drug administered in nonsustained-release form at 4-hr. intervals.

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Permeability of Double-Layer Films III

TSUNETO KURIYAMA, MICHIHARU NOBUTOKI, and MICHIO NAKANISHI

Abstract □ Moisture permeability of most double-layer films has a directional property. This "two-sidedness" may be brought about mainly by a change in the permeability coefficient as a result of the change in vapor pressure. To utilize this characteristic, it should be clarified as to how the permeability coefficient varies. For this purpose the differential permeability coefficient was calculated, making it easy to estimate the permeability of moisture under various conditions and making it possible to obtain the distribution of both vapor pressure and the water concentration in double-layer films. When the permeability on single films under various moisture conditions is given, the "two-sidedness" feature of double-layer films made from them will be grasped.

Keyphrases □ Double-layer films—theoretical considerations □ Films, double layer—moisture permeability □ Differential permeability coefficients—double-layer films □ Water concentration, vapor pressure—films

Previous reports (1, 2) dealt with variations of "two-sidedness" in the moisture permeability of double-layer films with changing conditions. It is very important to investigate the cause (or principle) of these phenomena. Rogers *et al.* (3) explained the two-sidedness skillfully, even though they did not classify such characteristics as were reported in a previous report (1). Their theory can be regarded as applicable to understand various types of two-sidedness and their behavior under changing moisture conditions. As stated in a previous report (2), the permeability coefficient, P, is not constant but varies with the moisture changes. Rogers *et al.* (3) introduced the concept of the differential permeability coefficient to solve this problem. The following theoretical considerations are mainly based on these ideas.

EXPERIMENTAL

The experimental method and the abbreviation for each film are the same as those in previous reports (1, 2).

Cell for Measuring Water Vapor Permeability—The cell and measuring method are modifications of those of Patel *et al.* (4). Permeation through a sample film was determined by measuring weight change of the cell at a certain condition.