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$$\frac{(^{13}C/^{12}C)_{sample} - (^{13}C/^{12}C)_{PDB}}{(^{13}C/^{12}C)_{PDB}} \times 1000$$

where PDB refers to the Pedee belemnite standard from the Pedee formation, Upper Cretaceous of South Carolina.
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14. The following $\delta^{13}C_{PDB}$ values were determined. The abbreviations are T (total organic fraction), S (soluble organic fraction), K (kerogen fraction), BY (approximate age $\times 10^9$ years), sample (sample number shown on Fig. 2).
1) Swaziland samples (cherts, 3.4 to 3.0 BY). Lower third Theespruit formation, 32 km southwest of Barberton: sample 5, T = −19.5, S = −26.1, K = −18.9 per mil; sample 3, T = −15.5, T = −14.8, T = −14.7, S = −25.5, K = −14.3 per mil. Upper third Theespruit formation, 32 km southwest of Barberton: sample 6, T = −15.1, S = −26.2, K = −15.8 per mil. Lower third Hooggenoeg formation, 27 km southwest of Barberton: sample 7, T = −28.8 per mil; sample 8, T = −28.4 per mil. Middle third Hooggenoeg formation, 38 km south-southwest of Barberton: sample 10, T = −32.1, T = −32.9 per mil. Middle third Kromberg formation, 29 km south-southwest of Barberton: sample 12, T = −33.0 per mil; sample 13, T = −27.5 per mil; sample 20, T = −30.6 per mil. Upper third Kromberg formation, 29 km south of Barberton: sample 18, T = −26.1 per mil; sample 19, T = −26.2 per mil. Zwartkoppie formation, 11 km northeast of Barberton: sample 22, T = −24.9 per mil. Zwartkoppie formation, 24 km east-northeast of Barberton: sample 26, T = −26.9 per mil. Zwartkoppie formation, 23 km east-northeast of Barberton: sample 27, T = −31.4 per mil. Lower third Fig Tree group, 10 km northeast of Barberton: sample 21, T = −28.7 per mil. Middle third Fig Tree group, 13 km south-southeast of Barberton: sample 28, T = −28.0 per mil.
2) Other Precambrian samples ($\delta^{13}C_{PDB}$ total organic fractions). Limestone: 3.3 to 2.8 BY, Bulawayan group, Rhodesia (three different samples), −33.5, −32.1, −32.5 per mil. Cherts: 3.3 to 2.8 BY, Bulawayan group, Rhodesia, −31.8 per mil; 2.6 BY, Keewatin, Schreiber, Ontario, −23.2 per mil; 2.2 BY, middle Fortescue group, Western Australia, −28.4 per mil; 2.2 BY, upper Fortescue group, Western Australia, −40.8 per mil; 2.0 BY, Transvaal System, South Africa, −28.0 per mil; 1.9 BY, Wittenoom Dolomite, Hamersley group, Western Australia, −29.0 per mil; 1.9 BY, Wittenoom Dolomite, Hamersley group, Western Australia, −31.2 per mil; 1.9 BY, Wittenoom Dolomite/basal Brockman Iron formation, Hamersley group, Western Australia, −30.2 per mil; 1.8 BY, middle to lower Brockman Iron formation, Hamersley group, Western Australia, −33.4 per mil; 1.8 BY, upper Brockman Iron formation, Hamersley group, Western Australia, −29.3 per mil; 1.8 BY, Gunflint Iron formation, Schreiber Beach, Ontario, −37.2 per mil; 1.8 BY, Gunflint Iron formation, Nolalu, Ontario, −34.1 per mil; 1.6 BY, Koolpin Chert, South Alligator group, Northern Territory, Australia, −31.0 per mil; 1.3 BY, Beck Spring Dolomite, California, −25.0 per mil; 1.0 BY, Skillogalee Dolomite, Yatina, South Australia, −21.0 per mil; 1.0 BY, Skillogalee Dolomite, Mundallio Creek, South Australia, −23.0 per mil; 1.0 BY, Skillogalee Dolomite, Depot Creek, South Australia, −25.2 per mil; 0.9 BY, Bitter Springs formation, Jay Creek, central Australia, −28.4 per mil; 0.9 BY, Bitter Springs formation, Ellery Creek, central Australia, −27.2 per mil; 0.7 BY, Conception group, East Newfoundland, −31.2 per mil.
3) Phanerozoic samples (cherts, $\delta^{13}C_{PDB}$ total organic fractions). Upper Cambrian, Catlin member, Windfall formation, Nevada, −29.4 per mil; Upper Ordovician, Maravillas Chert, W. Texas, −36.1 per mil; Upper Tertiary, Lost Chicken Creek formation, Alaska, −24.2 per mil.
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Decreased Concentration of Phenacetin in Plasma of Cigarette Smokers

Abstract. *The amount of phenacetin in plasma was determined in nine control subjects (nonsmokers) and nine subjects who smoked at least 15 cigarettes per day. The mean plasma concentration of phenacetin at 1, 2, 3½, and 5 hours after its administration was markedly lower in cigarette smokers than in nonsmokers. At 2 hours after the oral administration of 900 milligrams of phenacetin, the plasma concentration (± standard error) of unchanged drug was 2.24 ± 0.73 micrograms per milliliter in the controls and 0.48 ± 0.28 micrograms per milliliter in the smokers. The rate of excretion in urine of the major metabolite of phenacetin, N-acetyl-p-aminophenol, was the same in both groups. These results indicate for the first time decreased concentrations of a drug in plasma of persons who smoke cigarettes, and the results suggest that the decrease in the amount of phenacetin in plasma may result from increased metabolism of phenacetin in cigarette smokers.*

The administration to rats of many polycyclic aromatic hydrocarbons that are present in cigarette smoke (*1*) (such as 3,4-benzpyrene; 1,2,5,6-dibenzanthracene; and 1,2-benzanthracene) causes an increase in the activity of microsomal enzymes that metabolize certain carcinogens and drugs (*2*). The activities of benzpyrene hydroxylase and aminoazo dye *N*-demethylase, which are enzyme systems inducible by polycyclic hydrocarbons, were greatly increased in term placentas of individuals who smoke cigarettes (*3*). Increased benzpyrene hydroxylase activity was also found in the lung, the liver, the intestine, and the placenta of rats exposed to cigarette smoke (*4*).

We report here, for the first time, an effect of cigarette smoking on the plasma concentration of a drug. Phenacetin, widely used as an analgesic and an antipyretic, was selected for study because the conversion of this drug to its major metabolite, *N*-acetyl-*p*-aminophenol (APAP) (*5*), has been shown to be inducible in animals by polycyclic hydrocarbons (*6*).

Eighteen healthy volunteers, ranging in age from 24 to 35 years, included five female and four male cigarette smokers and five female and four male nonsmokers. The number of cigarettes smoked per day by the smokers varied from 15 to 40. The mean weight of the subjects (± standard error) was 123.2 ± 5.3 pounds (1 pound = 0.45 kg) for female smokers, 119.0 ± 4.9 pounds for female nonsmokers, 154.5 ± 9.8 pounds for male smokers and 159.0 ± 4.8 pounds for male nonsmokers. No drugs were taken by any subject for 2 weeks prior to the study. The ingestion of coffee and alcohol by these subjects was modest, and the amount consumed was the same for smokers and nonsmokers.

The cigarette smokers were not permitted to smoke for 8 hours preceding the administration of phenacetin and for the first 5 hours after drug administration. All subjects fasted overnight, except for water as they desired, and at approximately 8 a.m. on the day of the study they were given 900 mg of phenacetin (as a fine powder)

(7) with about 240 ml of water. No food or drink was permitted for the next 2 hours, except, again, for water after 30 minutes. Blood (25 ml) was drawn into a heparinized syringe just prior to the administration of phenacetin, and afterward at 1, 2, 3½, and 5 hours. The blood samples were centrifuged immediately after being collected, and the plasma was removed and stored at −15°C. Fully voided urine samples were also obtained at the above times, and, in addition, urine voided between 5 and 24 hours was collected. All urine samples were stored at −15°C. Urine concentration of APAP was measured as described (8).

The amount of phenacetin in plasma was measured by gas-liquid chromatography, with a recovery of greater than 90 percent. Plasma (3 ml), to which we added 2.0 ml of 0.1*M* KH_2PO_4–K_2HPO_4 (*p*H 7.4), was extracted with 30.0 ml of distilled benzene (spectranalyzed grade, Fisher) containing 1.5 percent isoamyl alcohol. The benzene phase was removed and washed with 5.0 ml of 0.1*N* NaOH (fluorometric grade, Harleco). A 25.0-ml portion of the benzene phase was evaporated to dryness under vacuum, at 35°C, on an Evapo-Mix (Buchler), and the residue was dissolved in 3.3 ml of distilled methanol (reagent grade, Merck). Chlorcyclizine (3 μg), as an internal standard, was added to 3.0 ml of the methanol extract, which was then evaporated to dryness under vacuum, at 35°C, on an Evapo-Mix. The residue was dissolved in 50 μl of distilled methanol.

A gas chromatograph (Hewlett-Packard model 402) equipped with a flame ionization detector and an integrator (Hewlett-Packard model 3370A) were used for phenacetin determination. A borosilicate glass column (1.8 m long, 3 mm inside diameter) was packed with Chromosorb W (AW-DMCS), 80/100 mesh, that was coated with 1 percent SE-30 and 1 percent Carbowax 20M (Applied Science Laboratory, lot 208-1737). Column temperature was maintained at 194°C, and the injector and manifold temperatures were held at 250°C and 270°C, respectively. Helium was used as the carrier gas at a flow rate of 50 ml/min.

The mean plasma concentrations of phenacetin in smokers and nonsmokers at 1, 2, 3½, and 5 hours after its administration are shown in Table 1. A significantly lower plasma concentration of phenacetin was found in the subjects who smoked. For example, the mean plasma concentration of phenacetin, 2 hours after its administration, was 2.24 ± 0.73 μg/ml and 0.48 ± 0.28 μg/ml in the controls and smokers, respectively. In four cigarette smokers, no measurable amount of phenacetin was found at any time, whereas measurable amounts of phenacetin were found in all nonsmokers. The highest concentration of phenacetin in the plasma of a nonsmoker was 7.38 μg/ml, while that in a smoker was 2.14 μg/ml. Although the concentration of phenacetin in plasma was decreased in smokers, the half-life of phenacetin in plasma was not decreased. This could be explained by (i) decreased absorption of phenacetin; (ii) increased volume of distribution; or (iii) enhanced metabolism in the gastrointestinal tract and/or during the first few passes through the liver. The rate of excretion of APAP in urine was evaluated to determine whether smoking decreased the absorption of phenacetin. Others (5, 8, 9) have shown that after oral administration of phenacetin, an average of about 75 percent of the dose is excreted in urine in 24 hours as conjugates of APAP. The data in Table 2 show the cumulative percent of the phenacetin dose excreted as APAP at 1, 2, 3½, 5, and 24 hours after phenacetin administration. No differences were observed in either the rate or the total excretion of APAP in the urine of smokers and nonsmokers. These observations suggest that the absorption of phenacetin or of its metabolite was the same in smokers and nonsmokers, and that the same percent of the dose (75 percent) was metabolized to APAP in both groups. This data, along with earlier studies indicating (i) a stimulatory effect of polycyclic hydrocarbons on phenacetin metabolism in vitro and in vivo in animals (6), and (ii) a stimulatory effect of cigarette smoking on carcinogen metabolism in man (3), suggests that the low concentrations of phenacetin in the plasma of smokers in our present study were due to increased metabolism of phenacetin, either in the gastrointestinal tract or during the first few passes through the liver. Consistent with this view are recent observations indicating that exposure of rats to cigarette smoke for 3 hours stimulates the total body metabolism of phenacetin that was administered 24 hours later (10). Three hours after the intraperitoneal administration of 150 mg of phenacetin per kilogram of body weight, 28 ± 3 μg of phenacetin per gram of total body tissue was present in control rats, while only 15 ± 1 μg of phenacetin per gram of total body tissue was found in rats previously exposed to cigarette smoke. Kampffmeyer has recently found, as we have, that large variations in individuals occur in the maximum blood concentration of phenacetin following oral administration of phenacetin, and he has suggested that phenacetin was metabolized to APAP faster in the individuals with the lowest phenacetin blood concentrations (11). Previous studies have shown that the rate of APAP elimination from plasma is slower than its rate of formation from phenacetin (9), and

Table 1. Plasma levels of phenacetin in cigarette smokers and nonsmokers at various intervals after the oral administration of 900 mg of phenacetin. Each value represents the mean ± S.E. for nine subjects. Results were analyzed by Student's *t*-test for paired data.

Subjects	Phenacetin in plasma (μg/ml) at intervals after administration (hours):			
	1	2	3½	5
Nonsmokers	0.81 ± 0.20	2.24 ± 0.73	0.39 ± 0.13	0.12 ± 0.04
Smokers	0.33 ± 0.23	0.48 ± 0.28	0.09 ± 0.04	0.02 ± 0.01
	$P > .05$	$P < .05$	$P < .05$	$P < .05$

Table 2. Cumulative amount of APAP excreted in the urine by cigarette smokers and by nonsmokers at various intervals after the oral administration of 900 mg of phenacetin. Each value represents the mean ± S.E., and *N* is the number of subjects whose urine was studied. Results were analyzed by Student's *t*-test for paired data.

Subjects	Percent of phenacetin dose excreted as APAP at intervals after phenacetin administration (hours):				
	1	2	3½	5	24
Nonsmokers	1.7 ± 0.5 ($N = 9$)	7.1 ± 1.4 ($N = 9$)	19.3 ± 2.9 ($N = 9$)	32.9 ± 3.6 ($N = 9$)	75.2 ± 5.2 ($N = 7$)
Smokers	1.3 ± 0.4 ($N = 8$)	8.2 ± 2.0 ($N = 8$)	21.6 ± 4.3 ($N = 8$)	30.5 ± 5.2 ($N = 8$)	73.8 ± 8.9 ($N = 6$)
	$P > .05$	$P > .05$	$P > .05$	$P > .05$	$P > .05$

therefore that the rate of excretion of APAP in urine cannot be used to determine the rate of phenacetin metabolism.

There is evidence suggesting that the disposition in vivo of compounds other than phenacetin may be affected by cigarette smoking. The duration of the paralysis elicited by zoxazolamine in rats and hamsters that were exposed to cigarette smoke was less than that found in rats and hamsters with no such exposure (*12*). An increased rate of excretion of nicotine metabolites in urine (*13*) and a decreased effect of pentazocine have been reported in human cigarette smokers (*14*). The results obtained here suggest a need to determine whether cigarette smoking influences the action and toxicity of phenacetin and other commonly used drugs.

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An Eocene Hystricognathous Rodent from Texas: Its Significance in Interpretations of Continental Drift

Abstract. *The earliest known representative of the fundamentally South American and African hystricognathous rodents has recently been found in the middle or late Eocene of southwestern Texas; this discovery supports the postulate of a northern and independent origin for the two southern groups and increases the evidence against mid-Tertiary trans-Atlantic migration of these rodents at a time when the South Atlantic was narrower than it is at present. The fossil seems to be related to the North American Eocene family Sciuravidae.*

One of the major problems confronting those interested in the evolution of the mammalian order Rodentia has been the origins and interrelationships, if any, of those members of the order, obviously not primitive, in which the angular process of the lower jaw has shifted laterally and originates from the side of the mandible lateral to the alveolus of the lower incisor, instead of arising from the ventral side of the alveolus, as in most members of the order. This condition, termed "hystricognathy," is normally associated with a forward expansion of the masseter muscle through the infraorbital foramen onto the snout, a condition termed "hystricomorphous." However, a number of hystricomorphous rodents are not hystricognathous, although all hitherto known hystricognathous rodents have been at least partially hystricomorphous.

At the present time, the hystricognaths are very abundant in South America (the suborder Caviomorpha) where they have been endemic since the early Oligocene, being known from the Deseado of Patagonia (*1*) and from equivalent beds of Bolivia (*2*). Some members of the suborder reached North America in late Pliocene or early Pleistocene times, the only successful immigrant having been the Canadian porcupine, *Erethizon*, now found over the entire continent as far north as Alaska and Labrador. Less abundant at the present time are the hystricognathous African rodents of the suborder Phiomorpha. These likewise appear in the early Oligocene [of Egypt (*3*)] but become highly diverse in the Miocene (*4*), and have survived to the present in considerably reduced diversity. Although phiomorphs have been largely restricted to Africa, they have recently been reported from the Miocene of the Aegean island of Chios (*5*). The African Bathyergidae, or blesmols, have been of doubtful relationships, but current work strongly suggests a phiomorph ancestry (*4*). A final group of hystricognathous rodents, the Hystricidae or Old World porcupines, are of completely unknown ancestry. Relationship to the phiomorphs has recently been postulated (*2*) and denied (*6*), in each case with no firm evidence.

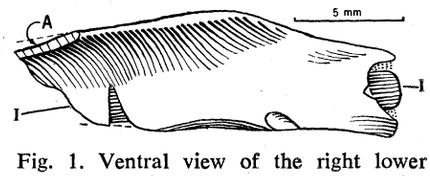

Fig. 1. Ventral view of the right lower jaw, lateral side to the top and anterior end to the right, Texas Memorial Museum No. 41372-179. *A*, angular process; *I–I*, projection of the vertical plane through the alveolus of the lower incisor.

It has been very clear from the fossil record that there has been no evidence of hystricognathous rodents in the richly fossiliferous deposits of Europe, Asia north of the Himalayas, or North America, until specialized members of the southern radiation appeared as obvious immigrants at varying but relatively recent times. Their simultaneous appearance in the early Oligocene of South America and Africa therefore raises important paleogeographic problems.

For many years, according to the standard explanation, the caviomorphs and phiomorphs were thought to have been derived from the European Eocene and Oligocene Theridomyidae, a group that was hystricomorphous but not hystricognathous. There are no great geographic problems (although there are morphologic ones) in deriving the African phiomorphs from such an ancestry, but there are obvious complications in getting the theridomyids to South America. The usual postulates vaguely proposed migration, either via Africa or direct from Europe, but the inability of all other terrestrial animals to use such a route militated against such a solution (*7*). It was therefore