showing physostigmine-induced theta responses were relatively immobile; they exhibited piloerection, defecation, shivering, and contractions of the facial musculature, best characterized as "cheek puffing." The four rats that showed running-induced theta, but no response to physostigmine, did not show much of an overt autonomic response to the cholinergic drug; they exhibited piloerection, but were relatively free of tremors.

Because of its toxicity, it was not advisable to administer physostigmine in doses higher than 1.0 mg/kg. However, two rats that had exhibited excellent theta responses with running but no response to 1.0 mg of physostigmine per kilogram did exhibit a prominent theta response to a dose of 1.5 mg of physostigmine per kilogram. There was never a case where a rat exhibited a physostigmine-induced theta response and failed to show theta with running.

Another test of the hypothesis that behaviorally induced hippocampal theta is a cholinergic response is to compare the effect of scopolamine, a known muscarinic blocking agent, on both physostigmine-induced and running-induced hippocampal theta responses. The results of this experiment are shown in Fig. 2. While scopolamine (10 mg/kg) had no discernible effect upon the hippocampal frequency spectrum when the rats were sitting quietly (Fig. 2, middle row, left), the synchronous theta responses to running and physostigmine (1 mg/kg) were completely blocked when challenged with scopolamine (compare top row with middle row in Fig. 2). This effect, which began 3 minutes after scopolamine administration (10 mg/kg, intraperitoneally) lasted for 40 minutes. It was seen in every animal (N = 10). Despite this dramatic block of behaviorally induced theta, scopolamine had no effect whatever on running in the treadmill. The behavioral topology of the scopolamine-treated rats was identical to the behavior of normal rats.

As expected, scopolamine (10 mg/kg) when mixed with physostigmine (1 mg/kg) completely blocked physostigmine-induced hippocampal theta responses (Fig. 2, middle row). This blockade had little or no effect upon the overt effects of physostigmine such as shivering, piloerection, and "cheek puffing." The lower dose (5 mg/kg) of scopolamine was not effective in blocking hippocampal theta responses.

Since Petsche *et al.* (*5*) have shown that destruction of the medial septal nucleus abolished physostigmine-induced hippocampal theta responses, the effect of septal lesions on drug-induced and behaviorally induced hippocampal theta patterns was compared. It was possible (N = 6) to completely abolish the theta response to both forced running and physostigmine with lesions of the medial septal nucleus. Lesions of comparable size that missed the target had no effect on behaviorally induced hippocampal theta responses (N = 3).

In one such case, the cingulum (a prominent pathway to the hippocampus) was destroyed. The pathway from the medial septal nucleus to the hippocampus was spared, and so was the response to running and to physostigmine.

It is possible that scopolamine could act directly on hippocampal neurons to block the behaviorally induced theta response. Feldberg and Vogt (*7*) and MacLean (*8*) have demonstrated that the hippocampus is rich in cholinergic neurons. Recently, Kuhar *et al.* (*9*) have demonstrated that medial septal lesions cause a profound reduction of acetylcholine levels in the dorsal hippocampus. There is evidence that the cells of the medial septal nucleus are cholinergic and act as pacemakers for the theta rhythm of the hippocampus (*5*). In addition, Friedman and Wikler (*10*) have shown that cholinergic agents acting directly upon cells of the posterior hypothalamus have a profound effect upon the hippocampal theta rhythm produced by means of electrical stimulation of the brainstem and hypothalamus. For this reason, it is not yet possible to specify where the scopolamine is acting to block the running-induced hippocampal theta response. The present findings are of considerable significance in that they provide a demonstration of a highly localized brain bioelectrical alteration, brought about by behavioral manipulation, that can be instantaneously induced, maintained for a considerable period of time, and can be related to the activity of a specific neurotransmitter.

HERMAN TEITELBAUM
JACK F. LEE
JAN N. JOHANNESSEN
Armed Forces Radiobiology Research Institute, Defense Nuclear Agency, Bethesda, Maryland 20014

References and Notes

1. C. H. Vanderwolf and W. Heron. *Arch. Neurol.* **11**, 379 (1964); C. H. Vanderwolf, *Psychol. Rev.* **78**, 83 (1971).
2. H. Teitelbaum and W. L. McFarland, *Physiol. Behav.* **7**, 545 (1971).
3. J. B. Ranck, *Exp. Neurol.* **41**, 461 (1973); J. S. Schwartzbaum and C. J. Kreinick, *J. Comp. Physiol. Psychol.* **85**, 479 (1973).
4. W. L. McFarland, E. Hedges, H. Teitelbaum, *ibid.* **88**, 324 (1975).
5. H. Petsche, C. Stumpf, G. Gogolac, *Electroencephalogr. Clin. Neurophysiol.* **14**, 202 (1962).
6. C. H. Vanderwolf, *J. Comp. Physiol. Psychol.* **88**, 300 (1975).
7. W. Feldberg and M. Vogt, *J. Physiol.* **107**, 372 (1948).
8. P. D. MacLean, *A.M.A. Arch. Neurol. Psychiat.* **78**, 113 (1957).
9. M. J. Kuhar, V. H. Sechy, R. H. Roth, G. K. Aghajanian, *J. Neurochem.* **20**, 581 (1973).
10. M. J. Friedman and A. Wikler, *Psychopharmacologia* **17**, 345 (1970).
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Floating Glacial Ice Caps in the Arctic Ocean

Abstract. *Two arguments are presented, one in favor of the existence of thicker ice in the Arctic Ocean during glacial time, and the other in favor of a full-fledged Arctic ice cap. The first is based on the Greenland air temperature record obtained from isotopic studies of the Camp Century ice core. The second is based on the oxygen isotope record of benthic foraminifera from a deep Pacific Ocean core.*

Although the idea of the areal expansion of floating ice in the Arctic Ocean and adjacent seas during glacial times receives frequent mention in the literature, only a few references to the possibility that much thicker ice existed can be found. Mercer (*1*) suggested that ice cover of the west Antarctic type may have developed in the Arctic Ocean during prolonged times of full continental glaciation. He also pointed out that in 1888 Sir William Thomson proposed to the Geological Society of Glasgow that a lapse in circulation between the Arctic Ocean and neighboring seas would cause it to be filled with solid ice. I would like to present two arguments in support of this old but not particularly fashionable idea. The first, which is quite firm, calls for thicker ice than at present, and the second, which is rather tenuous, calls for a very thick and largely buoyant "cap."

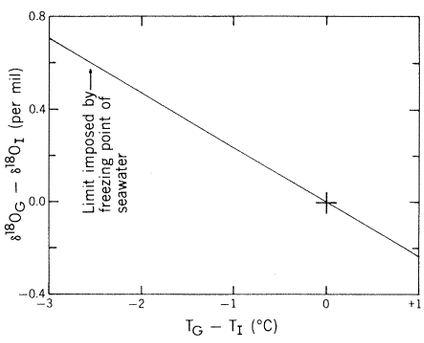
Under the climatic conditions which existed during glacial time, thicker Arctic ice is to be expected. To understand this we need to consider the factors controlling the present-day ice conditions in the Arctic and then project what might have been the case during times of major continental glaciation. In today's Arctic the ice stabilizes at a thickness of a few meters. The net loss of ice resulting from surface ablation in the summer is compensated by basal growth of sea ice during the winter. The rate of freezing beneath the ice depends on the rate of conduction of heat through the ice to the atmosphere. Hence the amount of winter growth is strongly dependent on ice thickness (other factors being equal, the growth

rate should vary inversely with the square of the ice thickness). On the other hand, the rate of summer ablation is independent of ice thickness and depends mainly on the summer air temperature. The ice thickness is thus self-regulating; it changes until winter growth just matches summer ablation. Different meteorological regimes would produce different steady-state ice thicknesses. These relations have been carefully defined by Maykut and Untersteiner (*2*). Today's conditions lead to thin ice cover because ablation exceeds snow accumulation.

The oxygen isotope record preserved in the Greenland ice cap suggests that the mean annual air temperature at the Camp Century drilling site averaged roughly 10°C colder during glacial than during postglacial time (*3*). If Arctic air temperatures were cooler by a similar amount, it is doubtful whether significant summer ablation occurred during glacial time. Snow accumulation may well have exceeded ablation. Under such conditions a net thickening of the ice from above would occur each year, just as it does today on neighboring Greenland.

Geologic evidence supporting this idea comes from the Barents Shelf. As early as 1900, DeGeer (*4*) envisaged an extensive ice sheet in the shallow waters around Spitsbergen. Fieldwork during the last decade or so provides strong evidence for a major ice sheet in the Barents Sea during the last period of continental glaciation (*5, 6*). Although this sheet rested on the generally shallow sediments of this broad shelf area, its existence adds weight to the argument that snow accumulation exceeded ablation in the Arctic Basin during glacial times.

The extent to which this thickening would proceed is not so obvious. It would depend on the degree to which ice was carried to the North Atlantic by surface currents. Today about one-tenth of the standing crop of floating ice in the Arctic Ocean is annually exported via the Greenland-Spitsbergen strait into the adjacent Atlantic, where it melts (*7*). This loss of ice by horizontal transport is about one-quarter of the loss by ablation. If ablation was negligible during glacial time and horizontal transport was as effective as today, then the steady-state ice thickness would have been about four times its present value. In order for an ice cap to grow, the exits from the Arctic would have to have jammed, greatly reducing the fraction of ice lost per year. Lowered sea level and the expanded ice caps on the Barents Shelf and in the Canadian Archipelago would completely seal off all but the passage between Greenland and Spitsbergen. This deep and wide



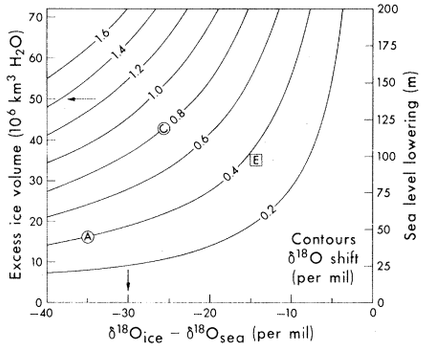


Fig. 1 (left). Temperature dependence of the equilibrium oxygen isotope fractionation factor between calcite and water. For each degree the water temperature falls, the ^{18}O enrichment in the calcite increases by 0.22 per mil. The temperature coefficient has been shown to be nearly the same regardless of the circumstances under which calcite precipitation occurs. Shackleton and Opdyke (*8*) were careful to analyze separated species rather than mixed benthics. Hence the 1.7 per mil shift they observed should not be influenced by any species effect. The maximum interglacial-glacial temperature shift in the deep Pacific is taken to be about 2.5°C. Such a cooling would bring the abyssal waters to their freezing point. Abbreviations: *T*,temperature; *G*, glacial; and *I*, interglacial. Fig. 2 (right). Contours of per mil enrichment of ^{18}O in seawater resulting from various combinations of excess glacial ice volume (in cubic kilometers and in meters of sea level lowering generated by the growth of this ice) and the average ^{18}O depletion in this ice. The square marked *E* is the original estimate made by Emiliani (*9*). Arrows indicate the maximum excess ice volume (left ordinate) and the maximum ^{18}O depletion in the ice (abscissa). The upper limit of ice volume is obtained from the outermost limit of mapped glacial extent and a mean ice thickness of 2 km (*15*). The upper limit of the ^{18}O deficiency is taken to be the average Holocene value for ice formed on the Greenland ice cap. The circle marked *A* is the value postulated for the ^{18}O shift caused by the thick Arctic ice cap proposed here. The circle marked *C* is the estimate adopted here for the size and isotopic composition of the continental ice present at the Wisconsin glacial maximum.

channel could only be closed by a buildup of ice far to the south in the shallower waters over the ridges connecting Iceland with Scotland and Greenland. While it is difficult to marshal any strong argument in favor of such jamming, it is not beyond the range of possibility. Thus, while demanding thicker floating Arctic ice, the colder glacial air temperatures recorded in the Greenland ice are not a sufficient condition for the growth of an Arctic ice cap.

A second line of reasoning based on isotopic evidence suggests thick ice. Shackleton and Opdyke (*8*) showed that benthic foraminifera from an equatorial Pacific deep-sea core record an interglacial-glacial change in the ratio $^{18}O/^{16}O$ of 1.7 per mil. Since bottom water is currently only a few degrees above its freezing point, most of this shift must have resulted from a change in the oxygen isotope ratio in deep-sea water rather than from cooling of the deep sea. The only possible cause for such a compositional change is the storage of ^{18}O-depleted water in glacial ice. The problem is that calculations based on estimates of the volume of excess glacial ice (over that present today) and of its mean oxygen isotope ratio yield values between 0.4 and 0.8 per mil for the isotopic shift in seawater (*9, 10*). Only by postulating the maximum possible lowering of the temperature of the deep ocean during glacial times (2.5°C, leading to an $^{18}O/^{16}O$ shift of 0.6 per mil) and by adopting the maximum excess ice volume estimates (50×10^6 km^3) and the maximum estimates of ^{18}O depletion in this ice (−30 per mil) can the 1.7 per mil shift measured by Shackleton and Opdyke be explained (0.6 per mil from cooling and 1.1 per mil from ice volume). The relations involved in this argument are shown graphically in Figs. 1 and 2.

The presence of floating glacial ice in the Arctic Ocean would help explain the discrepancy between the observed and predicted benthic ^{18}O shift. The existence of this ice would be recorded neither by end moraines nor by sea level lowering. The volume of 22×10^6 km^3 for the Arctic Ocean (*11*) provides an upper limit on the volume of floating ice in this basin. The lowest possible ^{18}O content is set by the value of −40 per mil observed in the Camp Century core for ice formed on Greenland during glacial time. Thus, up to about 0.6 per mil (see Fig. 1) of the benthic ^{18}O shift observed by Shackleton and Opdyke could result from the growth of an ice cap in the Arctic Ocean. If, for example, the oceanic ^{18}O enrichment created by this ice cap were two-thirds this limit, or 0.4 per mil, then the benthic shift could be accounted for as follows.

1) Excess continental ice ($\delta^{18}O$, −25 per mil; volume, 43×10^6 km^3; sea level lowering, 120 m), 0.8 per mil.

2) Arctic Ocean ice cap ($\delta^{18}O$, −35 per

mil; volume, 16×10^6 km^3; sea level lowering negligible), 0.4 per mil.

3) Deep ocean cooling (2°C), 0.5 per mil.

Total of three effects: 1.7 per mil.

Is there evidence in the Arctic sediments for thick ice? Certainly the absence of foraminifera and the very low detrital sedimentation rates found for sediments deposited in the Arctic during glacial time (*12, 13*) are compatible with this idea. Thicker ice would reduce light penetration and hence plant and zooplankton production. If ablation occurred mainly at the perimeter of the cap, then any windblown detritus accumulating on the ice surface would be carried to the south by the lateral flow of the ice and released there when melting occurred. However, as the severalfold thickening of the Arctic ice cover produced by lowered temperature alone would be adequate to explain the sedimentary evidence, the sedimentary evidence cannot be used to support the existence of an ice cap.

Clearly at this point there is only evidence that thicker ice existed in the Arctic Ocean during glacial time. Direct evidence for an ice cap is lacking. The observation that the large magnitude of the observed glacial-interglacial benthic ^{18}O shift demands more ice than can be accounted for by terrestrial moraines or sea level lowering provides only a reason for giving serious thought to the possibility that thick floating ice caps existed in both polar oceans during glacial times. If so, the growth and retreat of this ice add new elements to the global dynamics of glacial-interglacial change. The ingenious Ewing-Donn theory (*14*) focused so much attention on the possibility that the Arctic was ice-free during glacial time that the other extreme, an Arctic ice cap, has received too little consideration.

WALLACE S. BROECKER
Lamont-Doherty Geological Observatory and *Department of Geological Sciences, Columbia University, Palisades, New York 10964*

References and Notes

1. J. H. Mercer, *Palaeogeogr. Palaeoclimatol. Palaeoecol.* **8**, 19 (1970).
2. G. A. Maykut and N. Untersteiner, *J. Geophys. Res.* **76**, 1550 (1971).
3. W. Dansgaard, S. J. Johnson, H. B. Clausen, C. C. Langway, Jr., in *The Late Cenozoic Glacial Ages*, K. K. Turekian, Ed. (Yale Univ. Press, New Haven, Conn., 1971), p. 37.
4. G. DeGeer, *Geol. Foeren. Stockholm Foerh.* **22**, 427 (1900).
5. M. G. Grosswald, in *Climatic Changes in Arctic Areas during the Last Ten-Thousand Years*, Y. Vasari, H. Hyvärinen, S. Hicks, Eds. (University of Oulu, Oulu, Sweden, 1972), p. 205.
6. V. Schytt, G. Hoppe, W. Blake, Jr., M. G. Grosswald, *Int. Assoc. Sci. Hydrol. Publ. 79* (1968), p. 207.
7. E. Vowinckel and S. Orvig, *U.S. Dep. Commerce Publ. Meteorol. No. 44* (1961).
8. N. J. Shackleton and N. D. Opdyke, *Quat. Res.* **3**, 39 (1973).
9. C. Emiliani, *J. Geol.* **63**, 538 (1955).
10. W. Dansgaard and H. Tauber, *Science* **166**, 499 (1969).
11. H. U. Sverdrup, M. W. Johnson, K. H. Fleming, *The Oceans: Their Physics, Chemistry and General Biology* (Prentice-Hall, Englewood Cliffs, N.J., 1942).
12. T.-L. Ku and W. S. Broecker, *Progr. Oceanogr.* **4**, 94 (1967).
13. K. Hunkins, A. W. H. Be, N. D. Opdyke, G. Mathieu, in *The Late Cenozoic Glacial Ages*, K. K. Turekian, Ed. (Yale Univ. Press, New Haven, Conn., 1971), p. 215.
14. M. Ewing and W. L. Donn, *Science* **123**, 1061 (1956). It should be noted, however, that the revised Ewing-Donn theory of an open Arctic predicts freezing of the ocean surface layer during most of a glacial stage [W. L. Donn and M. Ewing, *Science* **152**, 1706 (1966)].
15. R. F. Flint, *Glacial and Quaternary Geology* (Wiley, New York, 1971).
16. Supported by NSF grant GA-27546. Lamont-Doherty Geological Observatory Contribution No. 2219.

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Detection of Mutagenic Activity of Metronidazole and Niridazole in Body Fluids of Humans and Mice

Abstract. *After humans were treated at therapeutic doses with the trichomonacide metronidazole (Flagyl) and the antischistosomal agent niridazole mutagenic activity was demonstrable in their urines when tested with the histidine auxotroph of* Salmonella typhimurium. *Both compounds were active in the host-mediated assay in mice, and evidence of activity was found in the blood and urine of mice treated with niridazole but not with metronidazole.*

Streptozotocin and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) have been evaluated for mutagenic activity by both the host-mediated assay technique and by analyses of the urine and blood of treated animals (*1*). Both compounds were active in the host-mediated assay. Mutagenic activity was detected with streptozotocin in both the blood and urine of treated animals; however, activity with MNNG could not be demonstrated in urine or blood of treated mice. Urines of treated animals have also been analyzed for mutagenic activity by a variety of indicators (*2*). Of particular significance is that the urines from patients treated with cyclophosphamide, an agent used in cancer chemotherapy, exhibited mutagenic activity (*3*). We now report our evaluation of the activity of two widely used commercial drugs, metronidazole (Flagyl) and niridazole, in the host-mediated assay as well as in blood and urine of treated animals; also we now have evidence of mutagenicity in the urines of patients treated with these drugs.

Niridazole and metronidazole were both active when directly tested against the histidine auxotroph of *Salmonella typhimurium* with the use of excision-repair minus, lipopolysaccharide-deficient tester strains (*4*). It is interesting to note that these heterocyclic nitro-containing compounds reverted different tester strains, with metronidazole reverting the base substitution strain TA1535, and niridazole reverting the frameshift mutant TA1538. Niridazole was mutagenically active at much lower concentrations than metronidazole, and was inhibitory to TA1538 at 100 μg per plate. Neither compound was affected by microsomal enzymes present in liver homogenates (*5*) (Table 1).

Although both compounds were active in the host-mediated assay, metronidazole was marginally active, exhibiting only a fourfold increase after 5 days of treatment at 400 mg/kg per day, whereas niridazole gave a tenfold increase after only a single dose of 10 mg/kg (Table 2).

With treated animals, blood samples

Table 1. Evaluation of the effect of metronidazole and niridazole when these drugs were incubated with liver homogenate (LH) (microsomal enzymes) and the mutation frequency of *S. typhimurium*.

Concentration (μg per plate)	MF* compound/MF control			
	Niridazole TA 1538		Metronidazole TA 1535	
	No LH	Added LH	No LH	Added LH
0.001	0.80	1.29		
0.01	1.08	1.14		
0.1	3.90	3.23		
0.2	9.69	9.64		
2.0	Toxic	Toxic		
50			1.60	1.16
100			2.00	2.23
500			4.25	5.09

*Mutation frequency, which is the ratio of histidine$^+$ revertants to the total number of bacteria.

Table 2. The results of the host-mediated assay with niridazole and metronidazole. The mice used were Jackson Laboratory $B_6D_2F_1/J$ females, weighing 20 to 25 g. Niridazole was given for 1 day, and metronidazole was given for 5 days.

Dose (mg kg^{-1} day^{-1})	MF compound/MF control	
	Niridazole TA 1538	Metronidazole TA 1535
1.00	1.42	
5.0	5.24	
10.0	9.35	
50		1.51
100	Toxic	1.68
400		3.78