Fig. 2. Measured time differences between master clocks at NBS, PTB, and TAO, as determined with the GPS common-view measurement technique. Also plotted is the Sagnac residual, which is the sum of the three pairs of time differences. The mean value of the Sagnac residual over the 90-day observing period was 5 nsec. UTC, universal time coordinated.

subtracted from the measured time difference (east clock minus west clock) in order to synchronize the clocks so they will measure coordinate time on the earth.

In the experiment reported here signals from GPS satellite vehicles 3, 4, 6, and 8 were utilized in simultaneous common view between three pairs of earth timing centers to accomplish the circumnavigation. The centers were the National Bureau of Standards (NBS) in Boulder, Colorado; Physikalisch-Technische Bundesanstalt (PTB) in Braunschweig, West Germany; and Tokyo Astronomical Observatory (TAO) (8). A typical geometrical configuration of ground stations and satellites, with the corresponding projected area, is illustrated in Fig. 1. The size of the Sagnac effect calculated from the expression above varies from about 240 to 350 nsec depending on the location of the satellites used in a circumnavigation carried out at a particular moment.

Enough data were collected to perform 90 independent circumnavigations. The data are plotted in Fig. 2, showing the time difference measured between each of the three sites via the GPS signals. The receivers used in this experiment automatically subtract the Sagnac correction, hence if the three pairs of measured time differences are added the result should vanish. The sum of the three pairs is also plotted in Fig. 2 as the Sagnac residual; this residual is obviously very near zero. The actual mean value of the Sagnac residual over the 90 days of observation was 5 nsec, which is less than 2 percent of the magnitude of the calculated total Sagnac effect.

Even though the atomic clocks used in the experiment were among the world's best, they are perturbed by natural random processes. The net time dispersion for this experiment attributable to these perturbations on the three clocks is about 2.5 nsec. The remainder of the

non-null result is explained by uncertainties in the propagation delays and in the ephemerides of the GPS satellites.

It is also of interest to observe the clock rate measurement consistency, as the sum of the three pairs of clock rate differences should also be zero. The residual in this case was two parts in 10^{15}. This measurement residual is one order of magnitude smaller than the inaccuracy of the best atomic clocks in the world. This leads to the very important conclusion that, with integration time of 1 week or longer, the GPS common-view measurement technique allows one, for the first time in the history of atomic clocks, to have access to the most accurate clocks in the world at any other site

without being limited by measurement uncertainties (2).

In conclusion, the theoretical predictions have been well verified by observation. Although the Sagnac effect has been observed frequently in laboratory settings, this is, to our knowledge, the first time it has been observed on such a large scale.

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Catastrophic Anoxia in the Chesapeake Bay in 1984

Abstract. In 1984, four climatic sequences combined to produce what may be a major anoxic catastrophe in the northern Chesapeake Bay, sufficient to severely threaten the major benthic species. These sequences are (i) the highest late-winter streamflow on record from the Susquehanna River watershed; (ii) streamflows from the Susquehanna River for the consecutive months of June, July, and August that are higher by 2 standard deviations than the respective monthly mean values measured over the last 34 years; (iii) a stationary high in August off the Atlantic Coast; and (iv) an absence of strong storm events in summer. An empirical equation is proposed for the prediction of the monthly trend of dissolved oxygen decrease in terms of a temperature-dependent subpycnoclinal respiration and a modified estuarine Richardson number. As of 23 August 1984, the summer pycnocline of the northern bay had eroded upward from its historically recorded depth below 10 meters to an abnormally shallow 5 meters, with higher stratification than in earlier years. Dissolved oxygen concentrations directly below the pycnocline decreased to zero during June, 2 months earlier than for previous wet years. At present, oxygen-deficient waters containing significant concentrations of hydrogen sulfide have penetrated into Eastern Bay and the Choptank and Potomac rivers. Because most remaining shellfish-spawning and seed-bed areas in these tributaries are located at depths between 4 and 8 meters, the continued absence of major destratifying events will prolong the present anoxic trend and may result in high benthic mortalities.

Low-oxygen concentrations in deep waters in many stratified lakes, fjords, and estuaries occur when the oxygen utilization rates exceed the oxygen replenishment rates across a pycnocline

brought about by turbulent vertical mixing. This phenomenon occurs annually in summer in the Chesapeake Bay (1–3). In 1976 an extensive anoxic catastrophe occurred in the New York Bight, leading

to high benthic mortalities (4, 5). It has been suggested that the magnitudes and areal extents of these summer anoxic events have increased over the past decades (3). In 1984 four climatic sequences combined to produce the potential for a major anoxic catastrophe in the northern Chesapeake Bay. The dissolved oxygen (DO) content in bottom waters directly below the pycnocline decreased to zero more than 2 months earlier than in previous wet years. By 23 August 1984, these waters were oxygen-deficient with significant concentrations of H_2S. The depth of the pycnocline has decreased from less than 10 m in previously reported years to between 5 and 6 m. The four sequences may be described as follows:

1) *High late winter streamflow*. The accumulation of precipitation during winter months in the watershed of the Susquehanna River determines the magnitude of the streamflow into the Chesapeake Bay due to ice melting in late winter. In 1984 there occurred the highest February streamflow (7.9×10^9 m³) on record (6). We have expressed the potential for a given streamflow to produce stratification by incorporating the mean depth of the water column into the Richardson number (7) to obtain a local estuarine Richardson number (LERN) (8):

$$\text{LERN} = \frac{\text{rate of delivery of buoyancy to a point along the axis}}{\text{rate of dissipation of buoyancy due to tidal, frictionally induced turbulent energy}} \quad (1)$$

$$\text{LERN} = \frac{(Q_f/A)(\Delta\rho_t/\rho_t)g}{<|U_t|^3>(C_D/<h>)} = 11.7Q_f\Delta\rho_t/\rho_t \quad (2)$$

Prior to ice melting, low streamflow combined with tidal turbulent mixing and storm events results in a weakly stratified system with LERN values around 10. After ice melting in February 1984, LERN was calculated to be 170.

2) *High spring-summer streamflows*. Streamflows during spring and summer are the result of precipitation in the watershed, usually peaking in April and exhibiting a minimum value in summer. However, in each of the months of June, July, and August 1984, streamflows from the Susquehanna River were significantly higher ($P < 0.05$) than the monthly means over the past 34 years of records kept by the U.S. Geological Survey (6). In Fig. 1A are plotted the mean monthly LERN values for 1984 for the Bay Bridge area, compared with the values for 1976 and 1983. The major differences

between 1984 and the earlier wet years are the higher values of LERN during May through August. From Eq. 2 it follows that, once stratification has been produced (high previous values of $\Delta\rho_t$), continued streamflow and increased insolation in summer can maintain the pycnocline as a steady-state stratification.

It is possible to develop an empirical equation to describe qualitatively the observed progression of oxygen depletion below the pycnocline by assuming the following: (i) that the total subpycnoclinal (including benthic) respiration, R, is temperature-dependent with a doubling of rate for a 10°C increase ($Q_{10} = 2$), characteristic of enzyme reactions. In any month j the mean monthly respiration is R_j; (ii) that the net loss of oxygen in bottom waters below the pycnocline is enhanced by increased stratification, which inhibits vertical mixing across the pycnocline; this enhancement factor is assumed to be proportional to LERN_j for any month j; and (iii) that the net loss of oxygen is cumulative.

If we assume that oxygen saturation in surface waters can be represented by a concentration of 9 parts per million, the oxygen concentration at any subsequent time can be given by

$$\text{DO (month } i) =$$

$$9 - \sum_{j=3}^{i} \frac{R_j \times \text{LERN}_j}{114} \quad (3 \leqslant i \leqslant 9) \quad (3)$$

where the number 114 has been calculated to make Eq. 3 agree with the 1984 data for the month of June, at which time DO was reduced to zero. In Fig. 1B are plotted the monthly values of DO calculated from Eq. 3 for 1976, 1983, and 1984, compared with measured values. Most earlier measurements of DO concentrations in subpycnoclinal waters have focused on the deep waters adjacent to the bottom sediments where the contribution to oxygen depletion by benthic respiration is a maximum. Since the depths of the sills of the major tributaries are relatively shallow, these more saline, anoxic, bottom waters are not usually horizontally advected into the tributaries. In Eq. 3 we are concerned with oxygen concentrations in waters directly below the pycnocline because these waters can be horizontally advected into the tributaries as bottom salt wedges. From Fig. 1B, it appears that DO below the pycnocline decreased to zero at the end of June 1984, 3 months prior to the expected time of the fall overturn observed in earlier years.

3) *Delivery of coastal waters into the Chesapeake Bay*. The density-driven, two-layered, stratified bay system in-

volves a net reverse flow of more saline coastal waters. This provides the physical basis for a suite of upstream transport and retention mechanisms for plankton (9). Beginning in August, persistent southwest winds from a stationary high forced additional high-salinity coastal waters into the bay below the pycnocline and provided additional energy for mixing of these bottom waters. This resulted in (i) increased salinities of bottom waters (by 10 per mil), (ii) enhanced mixing of these waters, and (iii) sufficient turbulence energy to erode the pycnocline upward from a depth of 10 to 5 m. These effects are documented in Fig. 2A at a survey station at 38°50'N, opposite Eastern Bay where DO was <3 ppm at 7 m and waters were oxygen-deficient at 8 m. Since the bay pycnocline is now higher than the depths of the sills of the major tributaries of the northern Chesapeake Bay, low-oxygen waters can be advected horizontally into the tributaries. In Fig. 2B are presented the results of a northern bay survey of isopleths of σ_t [$\sigma_t = 1000$ ($\rho_t - 1$)] and dissolved oxygen during 22 to 23 August. Extensive areas of the northern bay above the Bay Bridge, of Eastern Bay, and of the Choptank, Patuxent, and Potomac rivers are involved. Coincidentally, most of the remaining viable shellfish beds in the northern bay are located in Eastern Bay and the Choptank and Potomac rivers, including the St. Mary's River, a subtributary of the Potomac River.

4) *Inhibition of storm-event mixing of surface waters*. There has been an absence of strong summer storms in the Chesapeake Bay during 1984. Normally, severe storm events contribute to the transient downward erosion of the pycnocline, with consequent partial mixing of regenerated nutrient-rich bottom waters into the surface layer, supporting high summer phytoplankton production and the partial mixing of oxygen-saturated surface waters into bottom waters. In the summer of 1984 we measured abnormally low concentrations of dissolved total inorganic nitrogen and correspondingly low chlorophyll biomass in the surface waters of the northern bay.

The combination of the four climatic sequences has resulted in the present potentially catastrophic condition. The contributions of all four sequences appear to be necessary to produce this biologically severe threat. The climatic sequences described for the Chesapeake Bay region and the New York Bight (4, 5) may be correlatable on a global scale relating to El Niño and as such may fit a general pattern of forecasting potentials for catastrophic events in different estua-
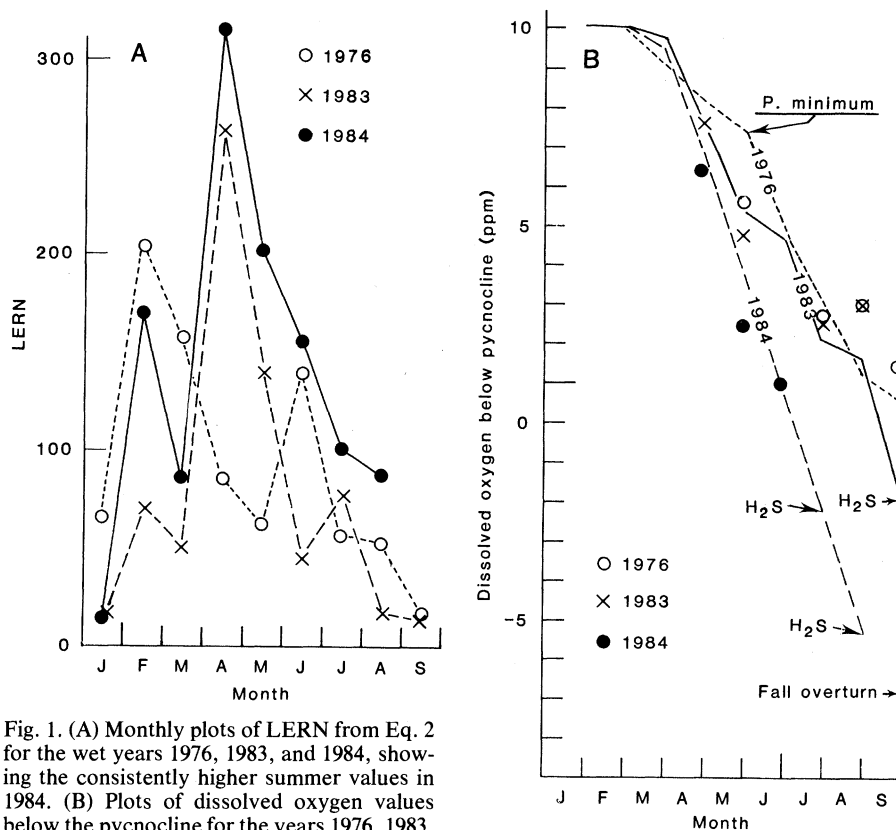
Fig. 1. (A) Monthly plots of LERN from Eq. 2 for the wet years 1976, 1983, and 1984, showing the consistently higher summer values in 1984. (B) Plots of dissolved oxygen values below the pycnocline for the years 1976, 1983, and 1984 predicted by Eq. 3. Values not directly measured are assumed to be greater than 5 ppm when significantly high concentrations of the dinoflagellate *Prorocentrum minimum* were measured below the pycnocline; these are indicated by an arrow followed by *P. minimum.* Values less than zero (oxygen-deficient) are indicated by an arrow attached to H_2S.
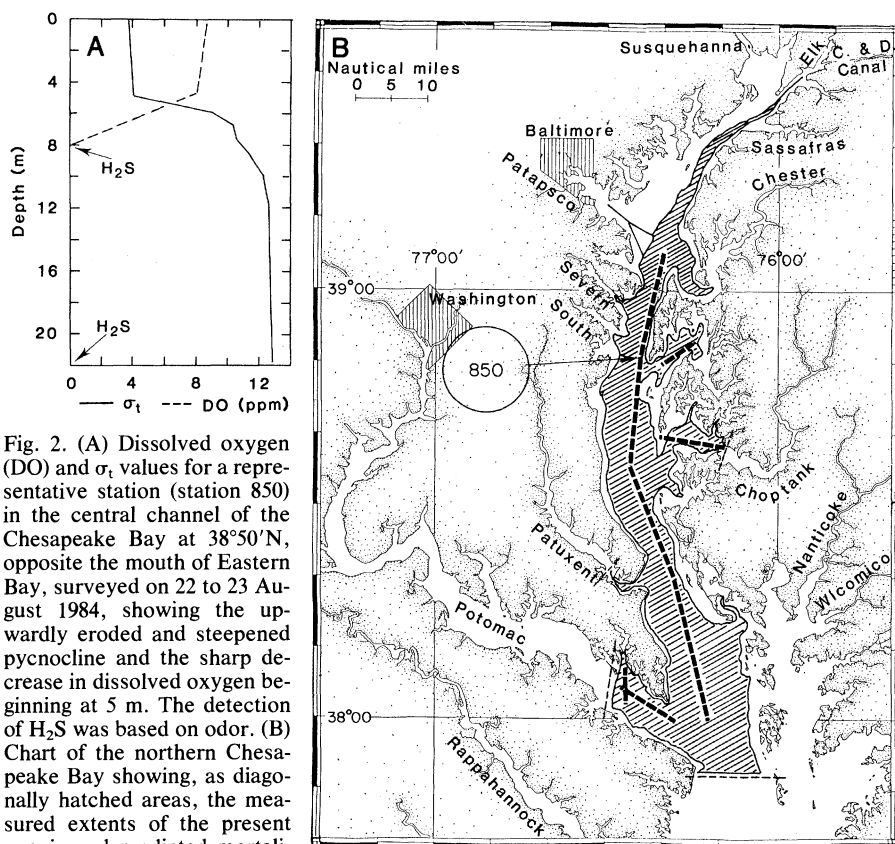

Fig. 2. (A) Dissolved oxygen (DO) and σ_t values for a representative station (station 850) in the central channel of the Chesapeake Bay at 38°50′N, opposite the mouth of Eastern Bay, surveyed on 22 to 23 August 1984, showing the upwardly eroded and steepened pycnocline and the sharp decrease in dissolved oxygen beginning at 5 m. The detection of H_2S was based on odor. (B) Chart of the northern Chesapeake Bay showing, as diagonally hatched areas, the measured extents of the present anoxia and predicted mortalities. The dashed lines indicate the specific transects along which vertical profiles of salinity, temperature, dissolved oxygen, dissolved inorganic nitrogen, and phytoplankton concentrations were measured. The dashed lines outside the hatched areas indicate the extent of the 5-m bathymetric contour.

rine systems (*10*). Strong stratification without wind forcing would not result in the significant penetration of deep anoxic waters into the more biologically productive tributaries. Wind forcing of coastal waters into the bay in the absence of strong density-driven stratification would further reduce the stratification of the entire water column without severe biological consequences. The most biologically significant aspect of the present condition is the upward erosion of the pycnocline, permitting anoxic and H_2S-containing waters to penetrate into the major tributaries. These waters, because of their shallow sills, would not normally be expected to be affected by anoxia in the deep central bay channel. In estuaries such as the New York Bight and the Chesapeake Bay there has been an environmental selection for benthic species that inhabit various depths and that can tolerate anoxia for various periods (*5*). Thus short periods of anoxia, just prior to the fall overturn of stratification and anoxia, give rise to relatively low mortalities. During extreme anoxic excursions, species at shallower depths, which are not normally exposed to and are generally not tolerant of anoxia, as well as more tolerant species at greater depths suffer high mortalities. This is now predicted for the oysters and clams in the tributaries of the Chesapeake Bay.

As of September 1984, at least one more month of hot weather, prolonging the anoxic period, is expected before the fall overturn. Continued subpycnoclinal secondary production, accelerated by organic nutrient contributions due to the mortality of sensitive species, may extend the area of anoxic bay waters below the pycnocline southward into the Virginia portion of the bay. Benthic populations in some regions of the southern bay may not survive. The present anoxia will presumably concentrate neritic organisms into the shallow surface layer of aerobic water where the primary production necessary for food chains is already low. In the absence of major destratifying events, the continuing stratification and anoxia should result in high mortality of the major benthic species, including oysters and clams in the northern bay tributaries, and severely stress the remaining neritic biota.

It is possible that recent anthropogenic eutrophication of the bay has resulted in the deposition of higher concentrations of particulate organic carbon in bottom sediments, with consequently higher rates of benthic respiration. Under these conditions, Chesapeake Bay waters as well as the New York Bight are more likely to exhibit greater anoxic excur-

sions during periods of strong stratification.

Note added in proof: A survey of oyster bars in the Choptank River on 6 to 7 September 1984 along a transect with bathymetries from 3 to 10 m revealed the mortality of all shellfish as well as their fouling organisms on bars below 6 m. Seed-bed areas and bars above 5 m were unaffected. This has since been verified by two independent surveys, involving personnel of the University of Maryland Sea Grant program and the Maryland Department of Natural Resources. During 4 to 12 September a precipitous drop in daily air temperatures by 12°C to below surface water temperatures produced sufficient instability to erode the pycnocline downward. This terminated the shallow pycnocline-anoxic water conditions in the tributaries, saving the remaining benthic stocks above 6 m. This finding raises two questions. Have earlier anoxic excursions occurred unnoticed and contributed to the decline of shellfish populations in the bay? Is the Chesapeake Bay ecosystem now less stable to extremes of climatic events than it was in the past?

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Circadian Timing of Cancer Chemotherapy

Abstract. *Animal studies have indicated that the time of administration of adriamycin and cisplatin, two widely used anticancer drugs, has a profound effect on their toxicity. This effect in cancer chemotherapy was studied in 31 patients with advanced ovarian cancer. Patients received at least eight monthly courses of adriamycin that were followed 12 hours later by cisplatin, with adriamycin randomly administered at either 6 a.m. or 6 p.m. The results show that in the group receiving adriamycin in the evening and cisplatin in the morning (i) twice as many patients required reductions in dosage and delays in treatment, (ii) four times as many treatments had to be delayed, (iii) drug dosages had to be modified downward three times as often, and (iv) even with more dose attenuation and treatment delays, treatment complications were still about two times more common as in the group receiving adriamycin in the morning and cisplatin in the evening. These findings show that the circadian stage at which anticancer drugs are given to patients should be carefully considered.*

Chronobiologic investigations have shown that the therapeutic indices of drugs can be affected by varying circadian drug timing. This phenomenon may be particularly important in anticancer chemotherapy. These powerful drugs can kill cancer cells but also kill or severely injure cells of normal tissues. Since the susceptibility of the normal tissues is rhythmically variable during the circadian cycle, whereas that of malignant tissue may be less so, the timing of chemotherapy may be an important element allowing greater therapeutic specificity.

The toxicity of at least 11 commonly used anticancer drugs has been shown in animal studies to depend on the time of administration (*1–5*). The therapeutic index of these agents and curability of several transplantable cancers in mice or rats are governed by the circadian time of drug treatment (*1, 2, 6*). Indeed, animal experiments had clearly indicated that the greatest toxicity of adriamycin is late in the activity cycle of the rodent and that of cisplatin near awakening (*7–11*). A test of whether circadian treatment time would affect human beings was designed.

A preliminary crossover study of 21 patients showed that post-treatment blood count fall and recovery, extent of decrement in creatinine clearance, and drug pharmacokinetics all differ substantially, depending on when patients are treated (*12–14*). Adriamycin given shortly before usual awakening (6 a.m.) and followed 12 hours later by cisplatin was better tolerated during the month after treatment than was this therapy when begun in the evening (usually 6 p.m.) (*15*). Because of these interesting acute toxicity results, a simple two-arm randomization of treatment timing was initiated.

Thirty-one women suffering from histologically verified ovarian cancer were each treated with an average of eight courses of adriamycin and cisplatin chemotherapy. None had received prior chemotherapy or irradiation therapy. All had widespread disease, which was limited to the abdomen in 22 (Figo stage 3), and which was also extra-abdominal in 9 patients (Figo stage 4). After patients were stratified by stage, the circadian treatment schedule was randomly allocated to each patient. The order of the two drugs and the span between them was kept constant. The planned doses were 60 mg per square meter of body surface for each drug. Circadian schedule A consisted of adriamycin infused between 6 a.m. and 6:30 a.m. (at or just before usual wakening) and followed 12 hours later by cisplatin from 6 p.m. to 6:30 p.m. Schedule B was administration of adriamycin at 6 p.m. and cisplatin at 6 a.m. This regimen was repeated approximately monthly to a planned total of nine treatments giving a total of 247 courses