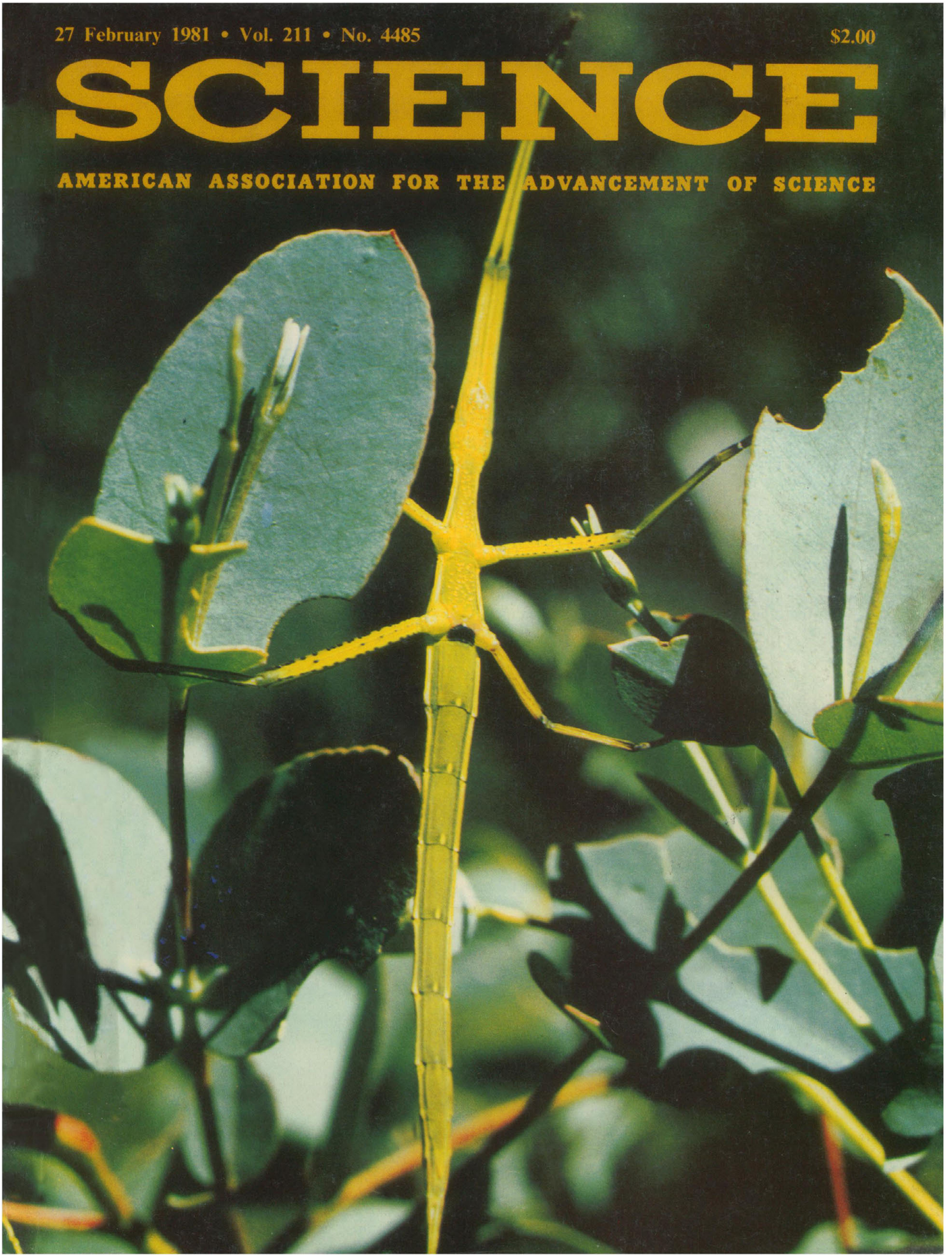
27 February 1981 • Vol. 211 • No. 4485 $2.00

# SCIENCE

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE



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**COVER**

Stick-insect, or phasmatid (*Didymuria violescens*). This is one of a large number of herbivorous insects that may cause considerable damage to *Eucalyptus* trees in southeast Australia, sometimes producing widespread defoliation. Many of these herbivore species have generalized diets, but may function as specialists in local communities. See page 887. [P. A. Morrow, Department of Ecology and Behavioral Biology, University of Minnesota]

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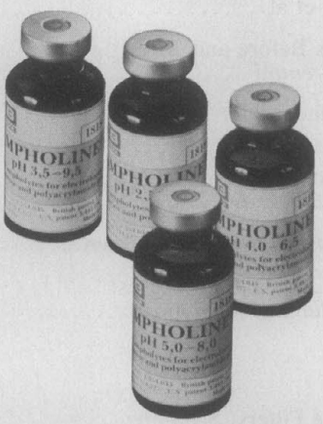

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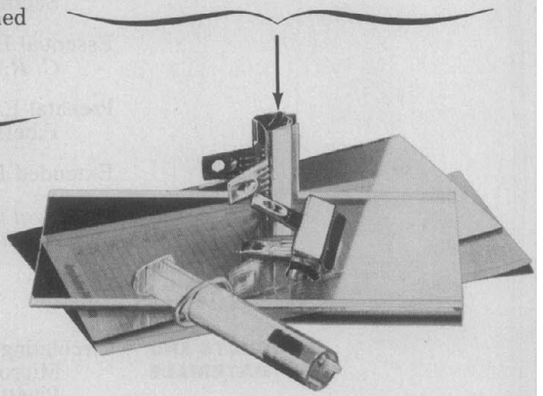


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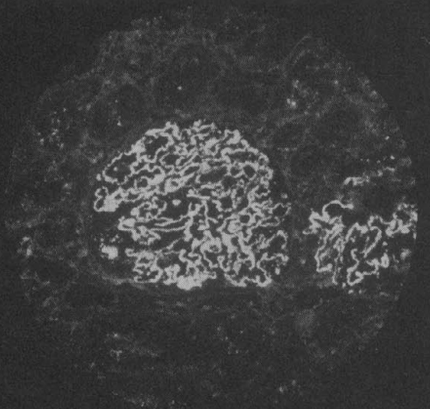

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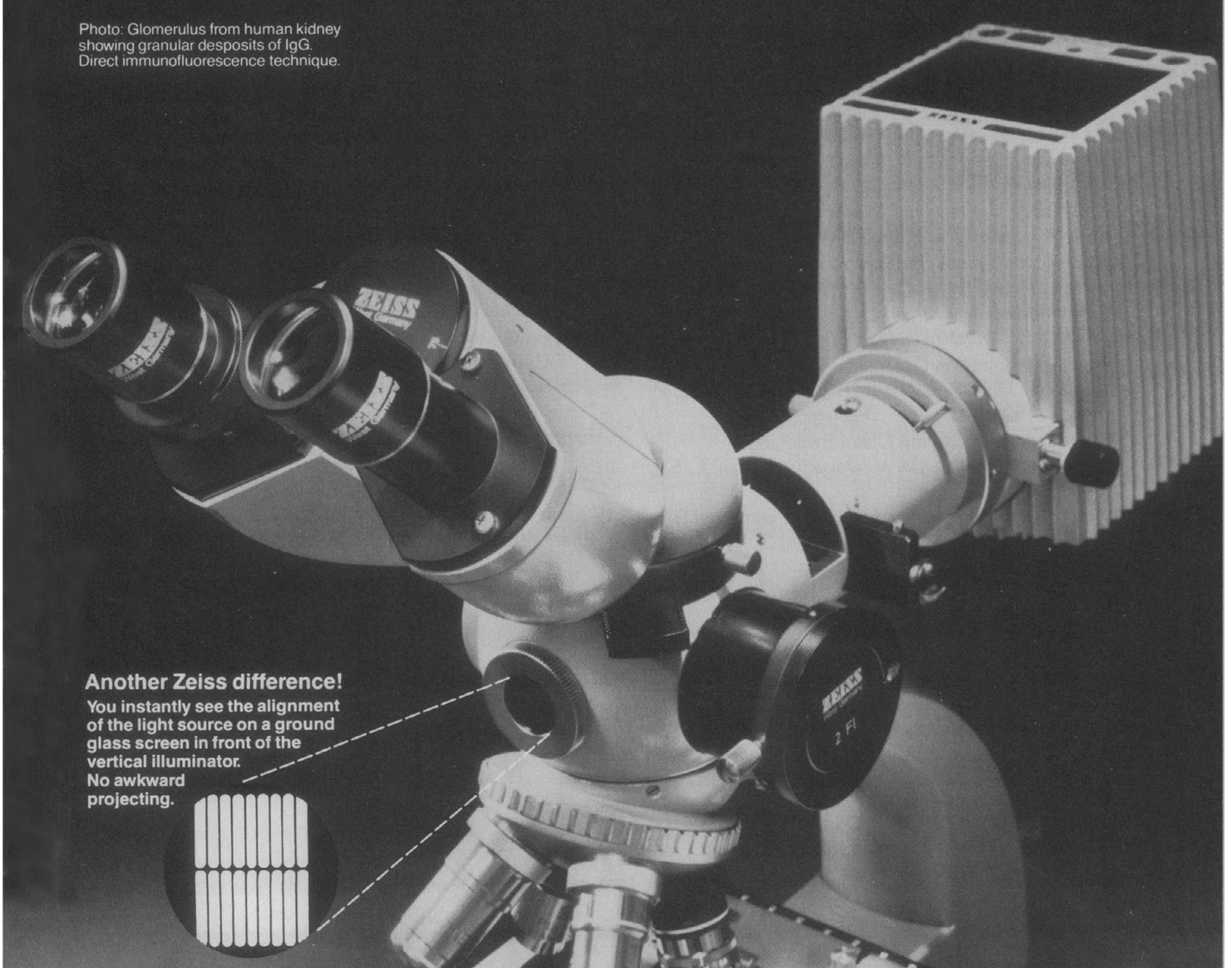
Photo: Glomerulus from human kidney showing granular desposits of IgG. Direct immunofluorescence technique.

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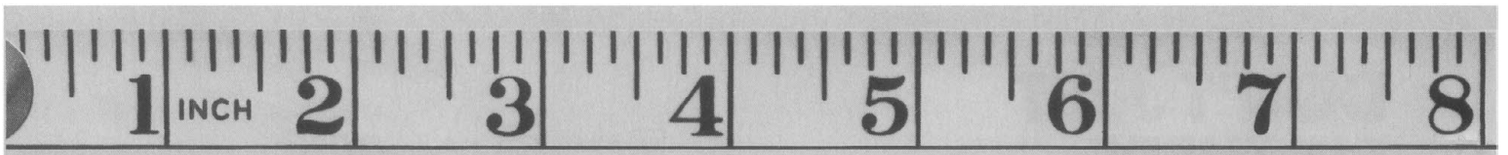


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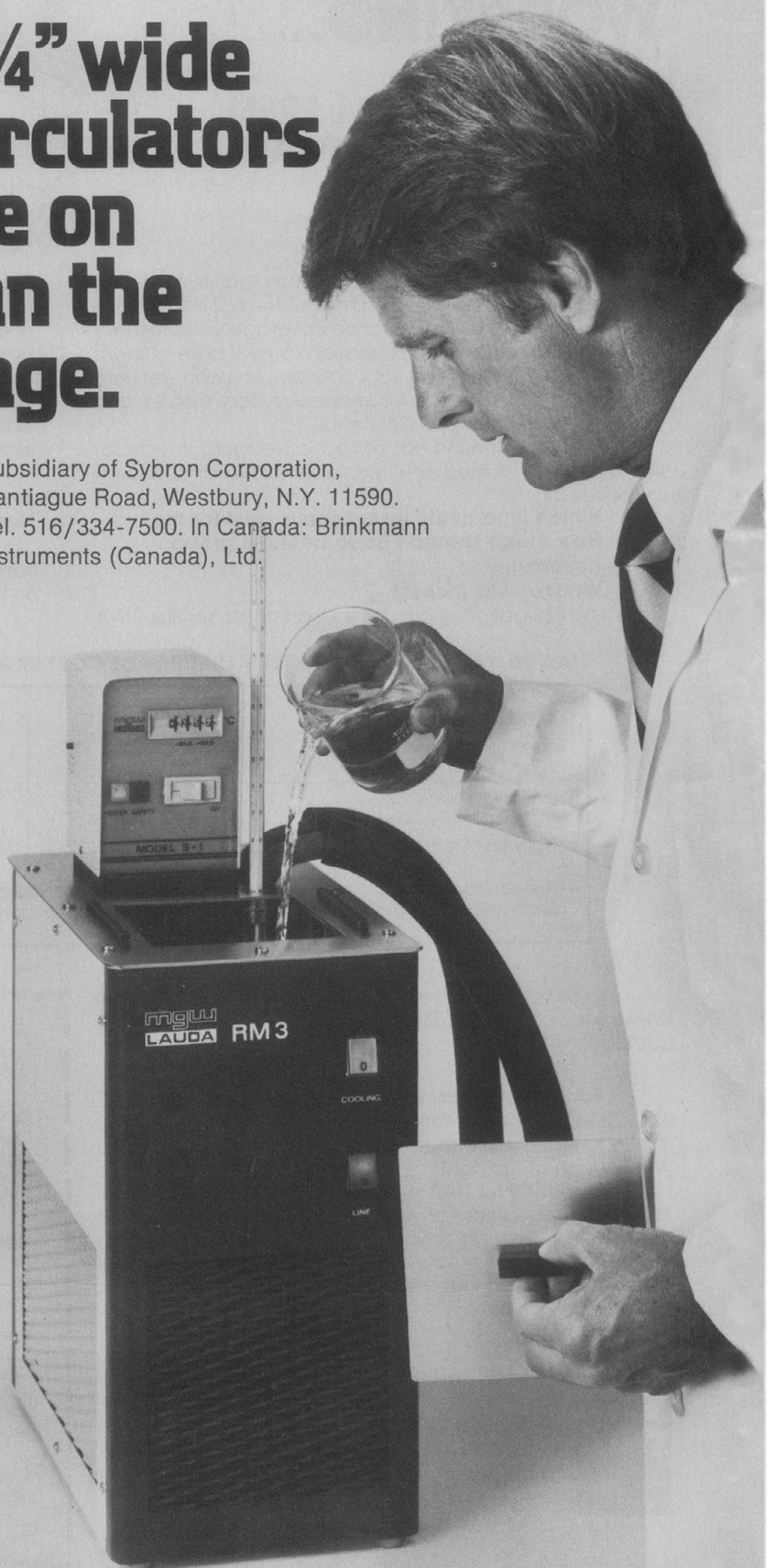


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## "Whistle-Blowee" Responds

The many scientists and other professionals in LMS Engineers, as well as myself, have read with absolute disbelief the 14 November 1980 article (News and Comment, p. 749) by Constance Holden entitled "Scientist with unpopular data loses job." Were it not for the correct spelling of our names and the photograph of our former employee, Morris H. Baslow, we would have believed we were reading an article about some other firm and individuals.

This biased and incomplete article has damaged our professional reputation, as well as that of the individual scientists who have worked with us for many years and adhere to the highest of professional standards. It is impossible to set all aspects of the record straight in this letter. The masthead statement regarding *Science*'s serving as a forum for, among others, the presentation of conflicting points of view, requires an article placing this matter in proper perspective (that is, a response from the "whistle-blowee"). Such a response is warranted all the more because we recently learned from Baslow that this matter has been under evaluation by the AAAS Committee on Scientific Freedom and Responsibility for some 6 to 8 months, including the interviewing of many parties, whereas our first contact with *Science* was scant days prior to the article's going to press.

Irresponsibility and lack of impartial reporting is evidenced by Holden's statement that "the commission [FERC (Federal Energy Regulatory Commission)] also wants to establish whether there has been any wrongdoing on the part of LMS Engineers." This issue has been specifically addressed in the findings of a 5-day hearing held before FERC Administrative Law Judge Stephen Grossman. Judge Grossman's order of 10 September 1980 states:

> A number of the participants to this proceeding have argued in the alternative that, if an attorney-client privilege exists, it has been waived. The finding above, that no privilege exists, eliminates the need to address questions of waiver. In fairness to Utilities and LMS, however, one matter raised in this context must be addressed. Several parties have claimed that Utilities waived all evidentiary privileges because they have attempted to use the privileges to shield wrongdoing. The record in this proceeding proves the contrary and, in fairness of the parties accused, that proof is noted here.
>
> The accusation of wrongdoing originated with Dr. Baslow's letter of October 8 to Judge Yost. In that letter, Dr. Baslow stated that 'I have known . . . that the density-dependent growth testimony in the utilities Hudson River . . . case is not valid.' Because LMS and Utilities knew of Dr. Baslow's research prior to the filing of the EPA testimony in question, the implication is that the Utilities knowingly filed false testimony before the EPA. Accepting this implication, of course, requires accepting the assumption that Dr. Baslow's studies vitiate the validity of the testimony filed before the EPA. Not even Dr. Baslow claims that his studies invalidate the EPA testimony. Testifying under oath at this proceeding, Dr. Baslow weighted his work this way. 'It is what it is and it points out a new area that must be considered when you deal with growth.' . . . Dr. Baslow rejected the proposition that his work 'completely devastated any major theories of compensation or density-dependent work.' . . .
>
> In fact, with regard to Dr. Baslow's work, the record reflects this. Dr. Baslow believed that his temperature studies had revealed an important relationship between temperature and fish growth. Certain scientists at LMS and with the Utilities believed he might have a point; others believed the contrary. Dr. Baslow pushed to have his findings reflected in the EPA testimony and was temporarily overruled. Counsel for Utilities suggested that, after further investigation, the studies might be used on rebuttal before the EPA. This is not then a case of fraud or false testimony. It was, until Dr. Baslow went public, merely a disagreement amongst scientists over the validity of a new and untested piece of information. No wrongdoing has been shown.

Clearly Holden had access to this order.

Other instances of biased reporting abound. The time apparently was taken to seek opinions on Baslow's integrity from those who aligned themselves with his "cause." Should not I, my partners, and LMS as a whole have been afforded the same? The legal steps taken by LMS and the utilities are characterized by delaying and maneuvering. Why not discuss with us the reasons for any legal steps we took, all of which were totally proper? Did Holden read Baslow's statements retracting his allegations of wrongdoing and employee discrimination? Had she done so, her characterization of the settlement reached might have left less an impression of begrudging acceptance, and more an impression of clear and unequivocal removal of issues of impropriety, leaving the matter solely in the realm of a scientific and technical dispute, which indeed it is. Holden lists the initial Labor Department finding but does not tell the reader that such a finding would play no part in the Labor Department hearing, a fact which Labor's letter indicates and which was clearly pointed out to Holden by our attorney.

In short, Holden plainly infers that "a little simple whistle-blowing"—going public with *claims* of misconduct by one's employer—is praiseworthy, even

when the claims are not true. Judge Grossman made the following comment during the aforementioned FERC hearing that I believe is relevant here.

> I suppose it is a syndrome that this country seems to have suffered from for some time popularly known as the 'Watergate Syndrome,' where there is leveled upon everyone regardless of what is being done, tremendous suspicion, especially anybody in the business or industrial community.
>
> There is cast upon those who come forward and say I am going public with something that my employer doesn't want me to tell anybody, a halo, a presumption of holiness. The person doing that must be right or else he would not do it. And anybody who suggests that he is not right must be wrong. You are dealing with a firm in which we do not even know whether a problem even exists in its whole history, or even contemplated that an employee might go away with documents that firm might consider proprietary or privileged or even if they considered the possibility of this hearing, nobody has yet asked Dr. Lawler about this. Nobody seems to care. What you are trying to do is set up a security system that perhaps would be appropriate for a strategic defense department site and implying that LMS should have had such a system and foreseen that an employee was going to try to walk off with something. I do not find that credible.

In the interest of an objective evaluation of the workability of employee protection laws, we deserve this opportunity to respond.

JOHN P. LAWLER
*Lawler, Matusky & Skelly Engineers,*
*One Blue Hill Plaza,*
*Pearl River, New York 10965*

### Galileo as a Scientist

The points I tried to make in my reply (Letters, 1 Aug. 1980, p. 544) to Whitaker (2 May, p. 446) were "unsupported" (Whitaker's letter of 10 Oct., p. 136), that is, unencumbered by footnotes, because I assumed that Whitaker was familiar with the underlying facts. This, apparently, is not the case. Let me therefore elaborate.

1) I admit that the copperplates of Galileo's drawings of the moon are more accurate, from the point of view of present-day knowledge, than the woodcuts, and those of my arguments which proceed from the latter are therefore rendered invalid—with a proviso to be spelled out in point 3 below.

2) However, not all troublesome aspects of Galileo's observations of the moon are thereby removed. For example, Galileo asks (*1*), "Why don't we see unevenness, roughness and waviness in the waxing moon's outermost periphery which faces west, in the waning

moon's other semicircular edge which faces east and in the full moon's entire circumference? Why do they appear perfectly round and circular?" Kepler wrote (*2*) (on the basis of naked-eye observations): "If you look carefully at the moon when it is full, it seems perceptibly to be lacking in roundness," and he answers Galileo's question by saying (*3*): "I do not know how carefully you have thought about this subject or whether your query, as is more likely, is based on the popular impression. For . . . I stated that there was surely some imperfection in this outermost circle during full moon. Study the matter and once again tell us how it looks to you" (*4, 5*).

3) If we want to know, as I do, whether Galileo proceeded in accordance with the rules that are today regarded as constituting proper scientific method or, as I shall express myself, whether he proceeded Scientifically (with a capital S), then we have to compare Galileo's drawings and statements with the evidence and the standards of accuracy of *his* time and not of *our* time. For example, we must ask: Given the accepted means and standards of observation, were his observations "facts" (that is, were they repeatable and were they theoretically well founded)? To find an answer we must compare Galileo's observations with other observations, made by astronomers of his own time, as well as with the theories held concerning the reliability of vision, especially of telescopic vision. If it turns out that the phenomena reported by him were not confirmed by anyone else and that there were no reasons for trusting the telescope as an instrument of research, but that many reasons, both theoretical and observational, spoke against it, then it was as unScientific for him to push these phenomena as it would be unScientific today to push experimental results that lack independent corroboration and are obtained by as yet untried methods—no matter how closely his observations approach our own. For to be Scientific means to behave properly with respect to existing knowledge and evidence and not with respect to the knowledge and the observations of an unknown future.

4) In order to find out what Galileo's contemporaries might have said about his observations of the moon, I used the woodcuts. Note that I did not try to argue that Galileo was a lousy Scientist because the woodcuts differ from modern pictures of the moon; such an argument would have conflicted with the considerations made in point 3 above which guided my research. My assumption was, rather, that the moon as seen by the naked eye looks very different from the woodcuts, that it might have looked equally different to Galileo's contemporaries, and that some of them might have criticized the *Sidereus Nuncius* on the basis of their own naked-eye observations. This assumption is still valid, for the woodcuts accompanied most editions of that book. Does it apply to the engravings as well? It does, as is shown by Kepler's criticism as reported in (*2*). In addition there were many reasons why the telescope was not uniformly regarded as a reliable producer of facts [these reasons, both empirical and theoretical, are assembled in my book *Against Method* (*5*)]. Whitaker's assertion that Galileo's drawings of the moon are of a high quality when compared with modern pictures is irrelevant to this discussion.

5) The case of Galileo's lunar observations is only a small portion of my argument to the effect that Galileo *did not* proceed in a Scientific manner and *could not* have made his discoveries had he proceeded Scientifically. He progressed by violating what some scientists and numerous philosophers regard as very important rules of Scientific method. As historical research proceeds and changes our views of the past, the evidence I use in my argument is of course going to change as well. I am perfectly willing to concede that this may make Galileo more Scientific in some areas; but more recent discoveries (starting with Lane Cooper's unraveling of the myth of the Leaning Tower experiments) have shown that the number of areas where he becomes less Scientific is on the increase. This does not turn Galileo into a bad scientist, for the practice of science is and always has been very different from what both scientists and philosophers of science have said about it. It only shows that being Scientific does not mean being a good scientist.

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2. *Johannes Kepler, Gesammelte Werke*, F. Hammer, Ed. (Beck'sche, Munich, 1939), vol. 2, p. 219.
3. *Kepler's Conversations with Galileo's Sidereal Messenger*, E. Rosen, Ed. and Transl. (Johnson, New York, 1965), p. 28.
4. In his observations Kepler was most likely aided by his polyopia, which also gave him good insight into the problems of visual (and telescopic) observations.
5. P. K. Feyerabend, *Against Method* (New Left Books, London, 1975), p. 127, footnote 24 and the literature given there.

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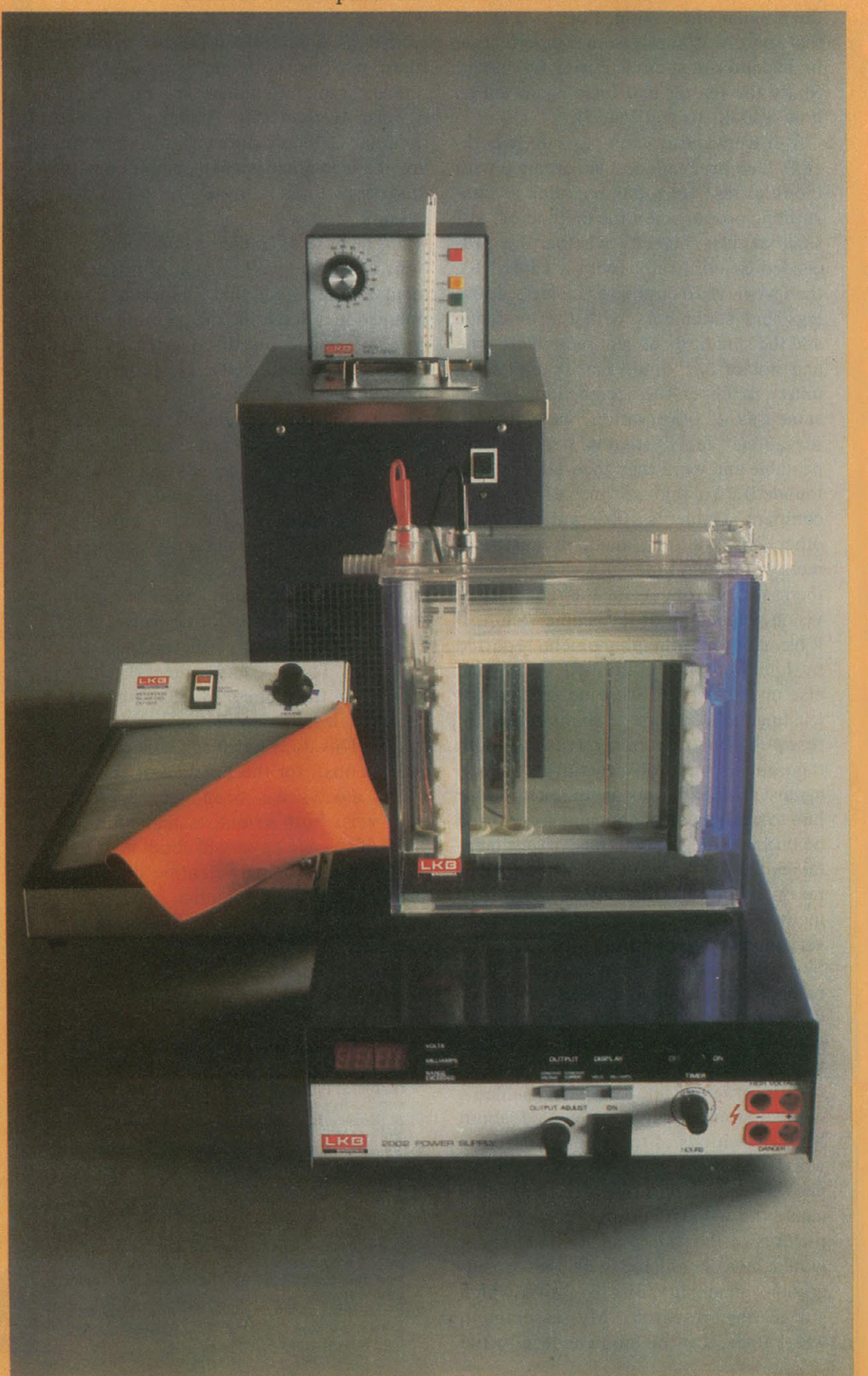

27 February 1981, Volume 211, Number 4485 **SCIENCE**



# The Threshold of Pain: Coping with Frugality

Early signals from Budget Director Stockman's stronghold are sending anticipatory shivers through the scientific community. News stories trumpet forthcoming cutbacks, rollbacks, and redirections of budgets for scientific and engineering research. How, when, and to what ends are the concerned societies to react?

Evidence accumulates that research budgets are expected to contribute to the inflation blood bank. Whether they will hemorrhage is a different matter. For the scientific community to react on warning would be precipitous and unthinking.

Some perspectives are in order. The national economy, in which science and technology play no trivial part, is struggling. The President has been in office less than a month. He has no science adviser at this critical juncture, which is itself a cause for deep concern, and the key scientific posts in the government are being kept on hold. To go after science budgets in the absence of these advisers may not be the best way to conduct decision-making, but public expectations for fiscal restraint are running high while the economic indicators are running down. Inflation has been no friend of science. There is ample justification for taking a firm and fast grip on the problem.

Whether research budgets will be treated too roughly, relative to everything else, remains to be seen. Science hardly can be considered untouchable relative to resource protection, transportation, income supports, foreign assistance, or other legitimate claims on the budget. What lies at the heart of the whole matter is the question of equity. That question cannot be answered until the full array of budget decisions sees the light of day. If science is clearly wronged, remedies can be sought from Congress. Just as there is a time for protest, there is a time for cool consideration of science's interests in the larger framework of the national interest. There is time. Fiscal year 1982 will not even begin for 7 months.

At best, the prospect for the President's tough economic program is not one of sweet national unity. If expansionary budgets are in bad favor, recessive budgets invariably are unpopular. Vested claims on benefits and subsidies besiege the whole budget, and despite a facade of consensus on the need for strong fiscal medicine, economies are resisted bitterly and usually beaten off. Such roughhouse politics do not rest well with science. Even less can be said for the spectacle of this community producing its own "hit list" of rival programs as candidates for execution in order to spare research. Things must not come to that.

The scientific societies face a trying test of their objectivity and political maturity. It is to be hoped that they will focus attention on the equities of the new budget policy and avoid pleading for immunity. What can be debated are the relative share of grief to be inflicted on science and engineering and where surgery is to be taken. The incidence of the cuts can and ought to be argued on the merits, and surely will be. For its part, the government should recognize the differences between investment in science and investment in capital assets like transportation. Science is a long-term creative process, and a multiyear retrenchment would damage seriously the nation's science and technology base. Investment for R & D has its place in supply-side economics. Capping their growth for the duration of the war on inflation would be shortsighted.

The new Administration has set itself a thankless and difficult task. It is entitled to a hearing. It will not have the last word. The system of checks and balances will see to that. As for the scientific community, how it approaches the budget crisis, by reflex or with reason, will tell us much about its ability to cope with stress.—WILLIAM D. CAREY

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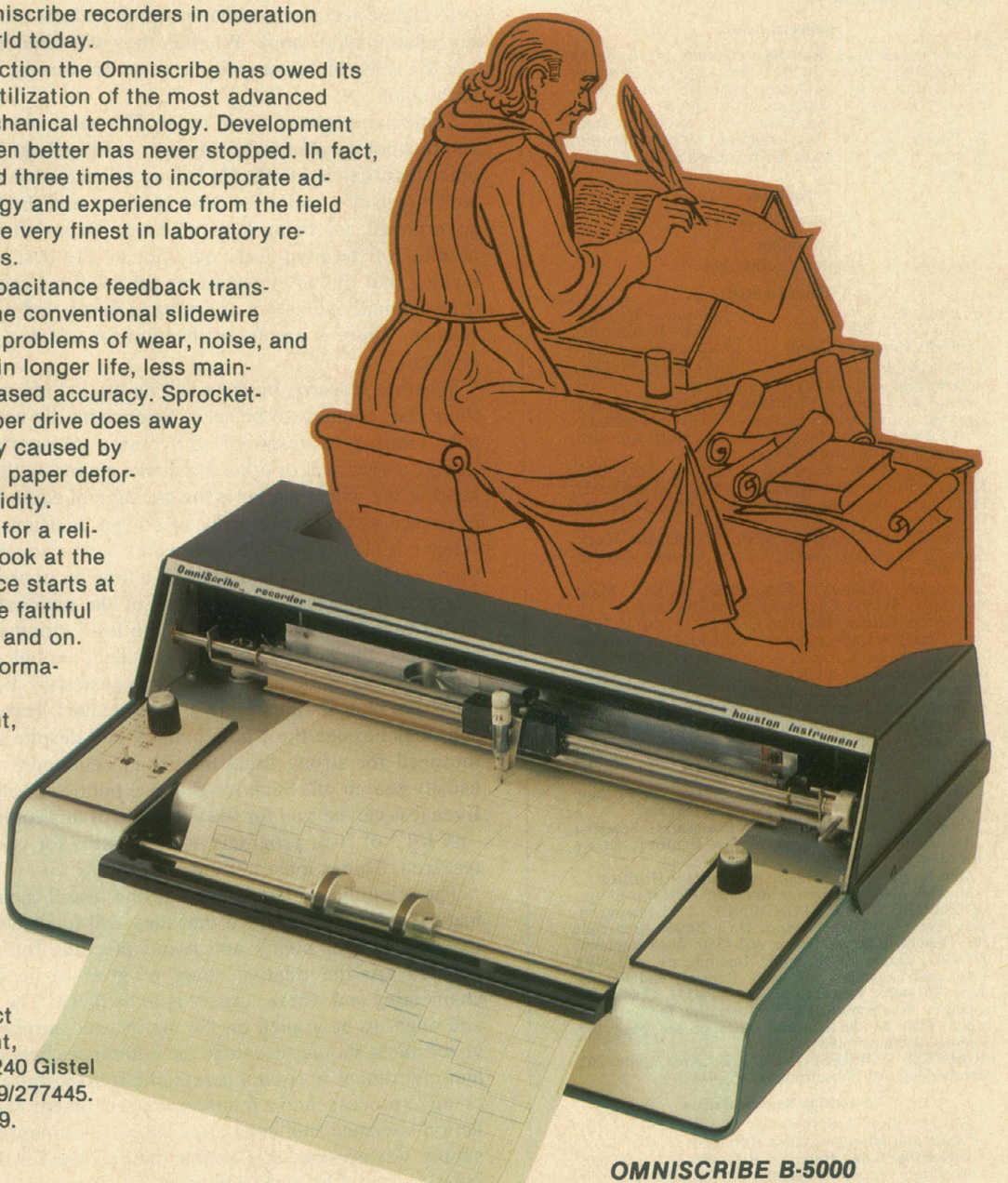


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8. In two cats from which ERG's were recorded 8 days after the operation, there was already some indication of ERG attenuation at the lowest spatial frequency tested.
9. In some recording sessions performed after the operation, the ERG in response to flickering light or to light flashes was somewhat larger in the right than in the left eye. A similar observation has been reported in human patients (*10*).
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29 September 1980

## Essential Hypertension: Central and Peripheral Norepinephrine

Abstract. *The concentration of norepinephrine in cerebrospinal fluid from patients with essential hypertension is higher than that from healthy normal volunteers, but the concentrations of norepinephrine in plasma from these groups are similar. This finding indicates that central nervous system noradrenergic hyperactivity occurs in essential hypertension but apparently is not reflected in abnormal function of the peripheral sympathetic nervous system in these patients.*

Evidence for a role of noradrenergic neurotransmission in blood pressure regulation is convincing (*1*). 6-Hydroxydopamine injected intracisternally selectively destroys brain catecholamine neurons, especially noradrenergic nerves, and prevents the expected onset of hypertension in several animal models (*2*). In hypertensive patients pharmacological data implicate noradrenergic hyperactivity (*1*). Antagonists of norepinephrine (NE) such as reserpine lower blood pressure, and agonists such as amphetamine increase pressure.

Peripheral sympathetic nervous system (SNS) function can be evaluated by measuring the amount of NE in plasma; NE is the primary neurotransmitter of the peripheral SNS (*3*). The literature is extensive yet remains controversial regarding increased NE concentrations in plasma of patients with essential hypertension (*4*).

Interest has increased in central nervous system noradrenergic regulation of blood pressure (*1*, *2*). Areas of the brainstem thought to be directly involved in regulation of blood pressure are densely innervated with neurons containing NE (*5*). Cardiovascular regulatory centers are anatomically adjacent to cerebrospinal fluid (CSF) (*5*), and the concentrations of NE in CSF should reflect noradrenergic neurotransmission in these areas of the brain (*6*, *7*). Since NE does not cross the blood-brain barrier, NE in plasma is not expected to contribute to measurements of NE in the CSF (*8*).

3 - Methoxy - 4 - hydroxyphenylglycol (MHPG), the primary catabolite of NE in the brain (*9*), is increased in CSF of hypertensive patients, and the concentrations of MHPG correlate positively with severity of the hypertension (*10*). Eide *et al.* (*11*) found higher concentrations of NE in the CSF of hypertensive neurological patients than in normotensive neurological patients. We previously measured NE in the CSF of 126 neurological patients who underwent a diagnostic lumbar puncture. In these patients NE concentrations correlated positively with blood pressure ($r = .41$, $P < .0001$) (*12*), but this correlation is partly attributable to patients with neurological diseases such as amyotrophic lateral sclerosis (ALS). Patients with ALS have high blood pressures and increased levels of NE in CSF, with the highest concentrations in the most severe ALS cases (*13*). We believed these results demonstrated enough evidence of a relationship between NE concentrations in CSF and blood pressure to warrant performing a lumbar puncture in patients who did not have a neurological disease but had essential hypertension and in healthy normotensive volunteers.

We measured NE in CSF and plasma from 11 patients with essential hypertension (three female) with a mean age (± standard error) of 48 ± 4 years and in nine healthy normotensive volunteers (four female) aged 44 ± 3 years; all subjects were Caucasian. Each patient and volunteer gave written informed consent to a protocol approved by the Human Research Review Committee of the National Institutes of Health (NIH). These subjects were admitted solely for the present study and none had a neurological disorder. All secondary forms of hypertension were excluded by history, physical examination, measurements of urinary and plasma aldosterone, serum chemistries, and performance of rapid-sequence intravenous urography. Renal arteriography and renal vein renin sampling revealed no abnormalities in selected patients. Blood pressures measured by auscultation or Arteriosounde (Roche) of the hypertensive patients were consistently above 140/90 mm-Hg (mean, 155 ± 5/95 ± 4) as determined three to four times daily by the patients at home or as outpatients by one of us (H.G.G.) at NIH. Each normal volunteer had blood pressure consistently below 130/85 mm-Hg (mean, 116 ± 3/73 ± 3) and had no significant medical or psychiatric illness as determined by negative history, physical exam, laboratory chemistries, and chest x-ray. No subject took medication for at least 2 weeks before admission to a metabolic ward at NIH for evaluation of their peripheral SNS function (*3*) and a lumbar spinal tap (*6*, *7*). We controlled for both the circadian rhythm and the rostrally increasing gradient of NE in human lumbar CSF (*6*, *7*). Subjects were given the same low monoamine diets for 7 days before they underwent a lumbar spinal puncture. The puncture was performed by the same neurologist (R.J.P.) under identical conditions as to time of day (8 a.m.), posture (sitting), and restrictions of all food and absolute bed rest for 8 hours before the puncture. Of the CSF from the lumbar tap needle, the portion between 16 and 20 ml was collected into a tube containing 10 mg of ascorbic acid, frozen immediately on dry ice, and stored at −70°C. The immediate use of ascorbic acid and dry ice differs from the procedure previously used to preserve and freeze CSF samples from schizophrenic and healthy control subjects (*7*). Details of the effects of technical differences in preserving and freezing CSF (on the content of NE in the CSF) are discussed elsewhere (*14*).

On another day during the same hospitalization period, to evaluate peripheral SNS function, 18 subjects had blood withdrawn from an indwelling heparin-lock while they were in the supine position at least 20 minutes after venipuncture, again after standing for 5 minutes, and finally after an additional 5 minutes of standing while performing an isometric exercise with a hand dynamometer (*3*). When all subjects had been studied (within 8 weeks), NE was measured in each sample on the same day in one radioenzymatic assay (*3*, *6*, *7*). NE does not deteriorate in plasma or CSF stored at −70°C for 6 months (*3*, *6*, *7*).

Concentrations of NE in CSF of patients with essential hypertension were significantly higher ($P < .02$) than in the normotensive volunteers (Fig. 1). Since these measurements were made from a portion of CSF from a lumbar spinal tap, the present difference between groups may reflect a larger difference in ventricular fluid and in actual NE release.


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Table 1. Pearson correlation coefficients.

| NE | N | NE in CSF | | Mean blood pressure* | | Age | |
|---|---|---|---|---|---|---|---|
| | | r | P | r | P | r | P |
| CSF | 20 | | | .45 | < .05 | .52 | < .02 |
| Plasma† | 18 | .73 | < .001 | N.S. | | .64 | < .005 |

*Mean blood pressure = (systolic − diastolic)/3 + diastolic. †The norepinephrine (NE) in plasma was measured while subjects were in a supine position.

We were unable to demonstrate differences between hypertensive and normotensive groups in concentrations of NE in plasma under conditions of supine rest or orthostatic or isometric exercise stresses (Fig. 1). As expected and previously noted (*3*), standing and performing an isometric handgrip (Fig. 1) significantly elevate plasma concentrations of NE similarly in both groups (supine to standing, $P < .01$; standing to hand squeeze, $P < .025$; paired $t$-test). Nor could we detect any differences in NE levels in subgroups of the hypertensive patients when they were divided according to high, normal, or low renin subgroups (*15*) or according to whether their blood pressure was sensitive to salt-loading [infusion of 2 liters of 0.9 percent saline during a 4-hour period (*16*)]. Our values for plasma NE are similar to those reported previously for different groups of hospitalized hypertensive and normotensive subjects (*17*) in which no differences were found between groups.

Data from all subjects were examined for relationships between variables. A multiple regression analysis yielded an $R^2$ of .60 ($P = .004$) when the amount of NE in CSF was the dependent variable, and the independent variables were age, mean blood pressure, and the amount of NE in plasma while subjects were in a supine position. The independent variables jointly can predict NE concentrations in CSF. The linear relationships between pairs of these variables were examined by using the Pearson correlation (Table 1). Concentrations of NE in both plasma and CSF correlate positively with age and with one another (*3*, *8*, *12*). Only NE in CSF correlates significantly with blood pressure. To examine more closely the contribution of blood pressure alone to the variability in the amount of NE in CSF, the partial correlation statistic was used. Accounting for the effects of age (keeping age fixed), the partial correlation coefficient between NE in CSF and blood pressure was not significant ($r = .36$, $P = .16$). In view of our report of a significant positive relation between NE in CSF and blood pressure (*12*), the present result may be due to the smaller number of subjects.

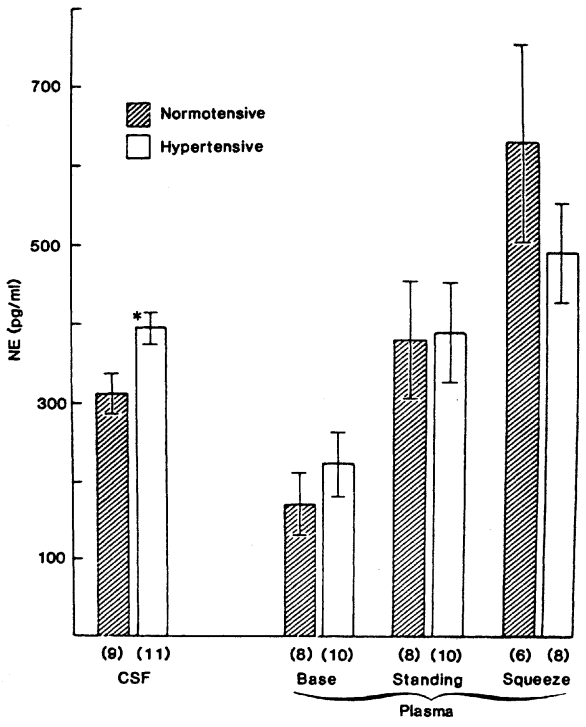


Fig. 1. Norepinephrine (*NE*) in cerebrospinal fluid (*CSF*) and in plasma of normotensive and hypertensive subjects. Plasma norepinephrine was measured while subjects were in a supine position (*base*), after standing for 5 minutes (*standing*), and after performing an isometric handgrip (*squeeze*) while standing for 5 minutes. Numbers in parentheses indicate number of subjects tested. Two subjects did not have blood drawn for plasma norepinephrine assay, and an additional four subjects did not perform the isometric squeeze exercise. Statistical comparison is by Student's two-tailed $t$-test; asterisk indicates $P < .02$.

The concentrations of NE in CSF of patients with essential hypertension reported here correlate positively but not significantly with age ($r = .43$, $P > .1$; $N = 11$), in contrast to the data of Eide *et al.* (*11*) which show a significant negative correlation ($r = -.83$, $P < .01$; $N = 7$). This relationship warrants further research since relatively few subjects were studied and an inverse correlation with age might indicate noradrenergic hyperactivity relatively early in the course of essential hypertension.

The partial correlation coefficient between NE in CSF and NE in plasma from subjects in a supine position (if one eliminates the effects of blood pressure and age) is significant for all subjects ($r = .64$, $P = .008$). This finding is difficult to explain in view of: (i) an apparently effective blood-brain barrier to NE (*8*), (ii) the increase of NE in CSF of the hypertensive group, but (iii) the lack of differences in plasma NE between groups. Concentrations of NE in CSF may be a more sensitive index of sympathetic activity because peripheral compensatory mechanisms may obscure modest changes in plasma NE levels. Accentuated release and clearance rates of NE peripherally may result in normal plasma NE concentrations (*18*). Despite the apparent normal responsivity of the hypertensive patients to standing and exercise, it is conceivable that an abnormally accelerated release response is masked by proportionally hyperactive clearance mechanisms (*18*).

Three current studies, including this report, examine the concentrations of NE in CSF in relation to blood pressure, and all show significant increases of NE in hypertensive patients (*11*, *12*). Some neurological diseases alter both NE in CSF and blood pressure (*13*, *19*); since some neurological patients were included in previous hypertensive and control groups, we did not know if this association of blood pressure with NE in CSF was a phenomenon influenced by neurological disease. The present data demonstrate that NE in CSF is higher in essential hypertensive subjects compared to healthy normotensive volunteers, but this might be a secondary phenomenon. Increased catecholamine release in anterior hypothalamus in response to systemic blood pressure elevation in cats (*20*) implies a secondary event. Abnormal periventricular epinephrine neurotransmission could explain the present findings; however, MHPG, the major metabolite of NE in brain, is also increased in the CSF of hypertensive patients (*10*), and the increase of both NE and MHPG suggests an acceleration in

the turnover of central NE in essential hypertension. The hypotensive effects of clonidine, a centrally acting $\alpha$-adrenergic agonist, are associated with decreases in the concentrations of MHPG in CSF of hypertensive patients (*10, 21*). Data from our laboratory indicate that, in humans, clonidine lowers both NE in CSF and blood pressure. These data are compatible with increases in the central release and turnover of NE in some patients with essential hypertension, suggesting that the decrements in blood pressure are associated with the lowering of central NE turnover induced with clonidine treatment. If a common abnormality exists for noradrenergic neurotransmission in essential hypertension, it is evident in the central nervous system. However, it was not reflected in abnormal peripheral SNS function in the hypertensive patients tested with the methodology described here.

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## Prenatal Exposure to Ethanol Alters the Organization of Hippocampal Mossy Fibers in Rats

Abstract. *Rats exposed to ethanol throughout their gestation were found to have abnormally distributed mossy fibers in temporal regions of the hippocampus. This demonstrates that prenatal exposure to ethanol causes alterations in neuronal circuitry that persist to maturity. Such defects may play a role in the mental retardation often observed in children with fetal alcohol syndrome.*

The potential teratogenic effects of ethanol have been suspected for centuries (*1*), but only recently has a characteristic group of anomalies been classified as the fetal alcohol syndrome (FAS) phenotype (*2*). Central nervous system dysfunction is particularly devastating in FAS. Although mental retardation and developmental delay are among the most consistent features, the cellular basis for such dysfunction is unknown.

The hippocampus is a brain region that is ideally suited for studying the effects of prenatal exposure to ethanol. It is unique in the precision of the laminar organization of its neurons. Since hippocampal afferents terminate on distinct segments of the dendrites of pyramidal and granule cells (*3–5*), subtle structural changes can be detected. Previous work showed that ethanol adversely affects the hippocampus in fetal and adult rats (*6, 7*) and humans (*8*). The present study shows that the exposure of rat fetuses to ethanol during a period equivalent to the first and second trimesters in humans results in abnormal neuronal circuitry in the central nervous system.

Nulliparous female Sprague-Dawley rats were mated with proven studs and isolated after vaginal smears showed them positive for sperm. One group was given free access to a liquid diet (Bio-

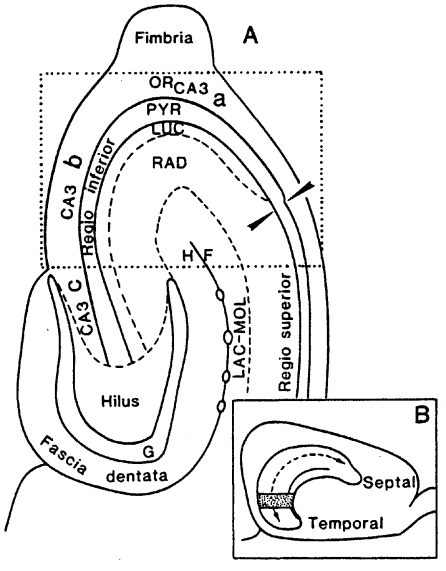


Fig. 1. (A) Schematic drawing of a hippocampal section through the horizontal plane. Abbreviations; *G*, stratum granulosum; *HF*, hippocampal fissure; *LAC-MOL*, stratum lacunosum-moleculare; *LUC*, stratum lucidum; *OR*, stratum oriens; *PYR*, stratum pyramidale; and *RAD*, stratum radiatum. Arrowheads mark the boundary between regio inferior and regio superior. The dotted square denotes the region shown in Fig. 2. (B) Drawing of the lateral aspect of the hippocampus. The shaded area indicates the midtemporal section of the hippocampus studied in this report. The dashed line with arrows indicates the septotemporal axis.


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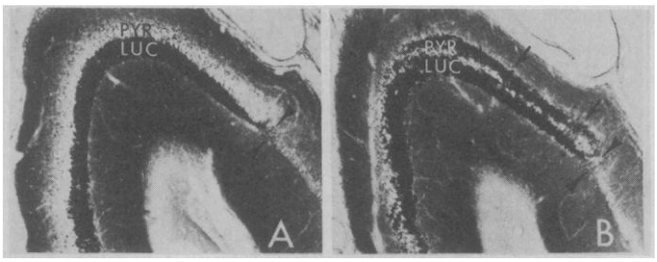


Fig. 2. Horizontal sections from equivalent septotemporal (midtemporal) levels of adult rat hippocampi stained with a modification of Timm's sulfide silver histochemical method. (A) Section from a control rat showing normal staining of mossy fibers. Note the lack of intrapyramidal mossy fibers. (B) Section from a rat exposed to ethanol in utero. The staining of the mossy fibers is conspicuously different: dense stain is present in the infrapyramidal region of regio inferior (arrows)—roughly equivalent to subfield CA3a—and the stratum lucidum is stained unevenly (×62).

Serv PR-11) containing 35 percent ethanol-derived calories. The liquid, delivered in calibrated feeding tubes, was given to the rats from days 1 to 21 of pregnancy, after which they were placed on a normal diet until term. Mean daily caloric intake was 66.37 ± 2.61 kcal, and mean daily ethanol consumption was 12.15 ± 1.15 g/kg (*9*). A second group was pair-fed an equal volume of the same diet, except that ethanol was replaced by isocaloric amounts of a solution containing maltose and dextrin (Bio-Serv). This controlled for possible neuronal alterations due to reduced caloric intake by the ethanol-fed mothers (*10*). At birth, litters from both groups were closely examined for external malformations, culled to eight pups, and cross-fostered to mothers on a normal diet (*11*). They were weaned at 22 days.

Each group of pups (experimental and control) was derived from four litters. After reaching 60 days of age, six animals randomly selected from each group and six normal rats were deeply anesthetized with sodium pentobarbital. Their brains were excised and processed according to a modification (*12*) of the Timm's sulfide silver procedure. Mossy fiber topography was examined in horizontal sections (Fig. 1A) at a midtemporal level along the septotemporal axis (Fig. 1B), where distal infrapyramidal mossy fibers are not normally found. In normal rats the densely stained, dark brown mossy fiber terminal field occupies much of the hilus of the dentate gyrus and then forms a hook-shaped suprapyramidal bundle that courses through the stratum lucidum (Fig. 2A) of regio inferior to approach the border of regio superior (*12–17*). An infrapyramidal bundle also exists and is confined primarily to an area near the hilus corresponding to hippocampal subfield CA3c of Lorente de Nó (*4*). A distal infrapyramidal terminal field of mossy fibers has been observed in an area corresponding roughly to subfield CA3a, but is limited to the rostral third of the hippocampus (*16, 17*).

Prenatal exposure to ethanol results in a dramatic change in mossy fiber topography. In all six ethanol-exposed rats we found a conspicuous band of distal infrapyramidal mossy fibers in hippocampal subfield CA3a at middle and more temporal levels of the hippocampus (Fig. 2). These aberrant fibers appeared to be a continuation of the rostral (normal) distal infrapyramidal band. In addition, there were often small, dark granules scattered through an infrapyramidal area corresponding to hippocampal subfield CA3b. The suprapyramidal mossy fiber band in the stratum lucidum sometimes appeared uneven. None of the pair-fed control animals had hypertrophied mossy fibers or other obvious alterations in mossy fiber topography.

The granule cells of the dentate gyrus are the major recipients of massive projections from the entorhinal cortex. They project to the hippocampal pyramidal cells, forming a major excitatory intrahippocampal pathway (*18*). There is evidence that the granule cells are involved in a behavior-dependent gating process that regulates the pattern of information processing to hippocampal field CA3 (*19*). The organization of the mossy fibers may play a physiologically significant role in the transfer of information from the entorhinal cortex to the hippocampus.

Alterations in mossy fiber topography in rats exposed to ethanol in utero are remarkably similar to those observed in rats treated with L-thyroxine (*14*) during early postnatal development and after being given hippocampal lesions shortly after birth (*15*). These postnatal treatments were performed after the formation of pyramidal cells but during the rapid development of dentate gyrus granule cells (*20*). In the present study, the ethanol exposure period included that interval during which virtually all of the pyramidal cells (the target cells for the granule cell mossy fiber axons) are formed but before a signficant number of granule cells appear (*20*). We do not know whether the effects reported here are a direct result of the ethanol treatment or represent a secondary effect occurring after an ethanol-induced change in endocrine development. Variations in the pattern of development of hippocampal pyramidal cells in different strains of mice also result in different patterns of mossy fiber organization (*21*). Thus, mossy fiber formation seems to be readily altered under a variety of conditions, although little is known about the mechanisms involved or the consequences of such alterations.

Previous studies have demonstrated that mossy fiber reorganization (such as that occurring after an entorhinal lesion) results in functional changes in remaining hippocampal afferents (*22*). Since the mossy fibers represent the only known major output from the granule cells, the alterations described here may disrupt hippocampal function. Prenatal exposure to ethanol at a dose slightly higher than that used in this study can also prevent the formation of a normal complement of hippocampal pyramidal cells (*6*). Thus alterations in neuronal connections, such as those between granule cells and pyramidal cells in the hippocampus, may have a profound effect on an area of the brain which, in humans, is thought to play a role in memory (*23*). These distortions in neuronal architecture may be responsible for some of the serious mental impairments, although one can only speculate about the specific causes of the mental retardation seen in FAS.

The human brain undergoes less postnatal development than the rat brain; indeed, the entire gestation period of the rat is only equivalent to the first and second trimesters in humans (*24*). It should also be noted that, except for one case (*11*), the aberrant mossy fiber connections were found in animals lacking obvious external malformations. While the toxicity of ethanol to the central nervous system may vary in different species (*25*), neurological screening of progeny born to mothers who consumed alcohol during pregnancy may be desirable even in the absence of other major FAS features. Additional research is needed to determine the minimal dose of ethanol required to produce aberrant neuronal connections and to ascertain whether there are critical periods during which ethanol is particularly dangerous to the fetal brain (*26*).

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