LETTERS AND CORRECTIONS

"The power and the beauty of science do not rest upon infallibility, which it has not, but on corrigibility, without which it is nothing."—Howard E. Gruber*

Letters submitted for publication must be typed double-spaced. Text length must not exceed 500 words, and no more than five references may be used. Complete references must be furnished, as specified in "Information for Authors" (page I-6). Specific permission to publish should be appended as a postscript. Publication depends on availability of space: We give preference to comment on recent content and new information. Letters for this section should be concise—the Editor reserves the right to shorten them and make changes that accord with our style.

Hepatitis B and Sexual Practices

TO THE EDITOR: Reiner and coauthors (1) present evidence for de facto parenteral transmission of hepatitis B through specific sexual activities in gay men and provide more information on the complex puzzle of disease and data collection in this population. We present four points for consideration.

First, in a study of sexual transmission of hepatitis A, Corey and Holmes (2) found the acquisition of hepatitis B significantly correlated with the frequency of anal receptive intercourse but not with analingus. This finding contrasts with the unpublished data cited by the authors on the risk of analingus.

Second, because the prevalence of specific sexual activities among series of gay men not studied clinically is not well documented, assigning relative risks to most sexual practices is difficult. Thus, when Reiner and associates (1) cite an estimated 40% incidence of morbid complications from anal intercourse in gay men, they overstate the support of their references. Owen (3) does not offer any incidence figures, and the data of Kazal and coworkers (4) were drawn from a proctologic practice, certainly not a representative sample of gay men. Bolling's report (5) of a low complication rate from anal intercourse, although drawn from a heterosexual female population, suggests caution in attributing morbidity to anal intercourse itself. Two of us helped prepare a detailed questionnaire that included questions on sexual practices, history of sexually transmissible disorders, and number of partners; it was completed by about 600 people who approached the Bay Area Physicians for Human Rights booth at the Gay Freedom Day Parade in San Francisco in June 1981. These data are being analyzed and will be prepared for publication soon.

Third, mention is not made of the very common practice of using saliva (usually the insertive partner's) as a lubricant in anal intercourse. This factor is significant for two reasons: HBsAg-containing saliva can invade anorectal mucosal sites of injury or ulceration without analingus, and saliva is a poor lubricant that probably permits anorectal mucosal injury more readily than when other lubricants are used.

Fourth, the presence of anorectal erosions in 13 of 22 patients (identical lesions in 12 of 13) of the authors' sample seems high if the patients were selected only by the presence of hepatitis B antigenemia. The authors' conclusion that these lesions are "sexually induced" is unwarranted by the data they present (if we are correct in assuming that by "sexually" they mean "traumatically" through anal intercourse). In the Patients and Methods section they note that time elapsed since passive anorectal intercourse was recorded for each patient, but this information is not provided in the Results section and may have been helpful. However, their finding does suggest a common cause that requires careful follow-up. Infectious causes of anorectal lesions must be separated from the possible physical consequences of various sexual practices. Although this separation cannot be definitive, because knowledge of the microbiology of anorectal disease in gay men is not complete, a more thorough answer could be obtained than the authors present.

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5. BOLLING DR. Prevalence, goals and complications of heterosexual anal intercourse in a gynecologic population. *J Reprod Med.* 1977;**19**: 120-4.

International Needs in Occupational Medicine

TO THE EDITOR: Since it was established in 1970 the National Institute for Occupational Safety and Health (NIOSH) has made a major contribution to the scientific and technical understanding of work-related risks and hazards. Its findings, standards, and recommendations are used all over the world. Smaller countries with programs of occupational health and safety protection, which cannot mount a full-scale scientific research effort of their own, rely on NIOSH studies and materials.

We call attention to the fact that reductions in NIOSH funding have an impact well beyond the borders of the United States, a fact which may not be well understood by Americans. We do not believe that in doing so we are intervening in a domestic matter. Rather, we feel the obligation to inform those who may read this statement that the control, prevention, and reduction of occupational illnesses and accidents is an international issue to which NIOSH makes a major contribution. We respectfully request that this be brought to the attention of those who will determine the future level of NIOSH activities.

[Submitted by VICTOR W. SIDEL, M.D. and SUMNER M. ROSEN, PH.D. on

*GRUBER HE. The origin of the origin of species. Review of *Darwin and the Mysterious Mr. X: New Light on the Evolutionists.* By EISELEY L. *The New York Times Book Review.* 1979 July 22:16.

behalf of 53 signers abroad: Australia, 1; Canada, 6; Denmark, 15; England, 1; Finland, 2; Germany, 6; Malaysia, 1; Norway, 6; Sweden, 15. Names of the signers are available from Dr. Sidel.]

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Aspirin, Dipyridamole, and Thrombotic Thrombocytopenic Purpura

TO THE EDITOR: The judgment as to what constitutes the best treatment for patients with thrombotic thrombocytopenic purpura (TTP) is based on empiric evidence rather than on the results of controlled therapeutic trials. Unfortunately, TTP does not lend itself to such trials because of its rarity and rapidly fatal course, and because commonly accepted treatments are relatively innocuous. Attempts to evaluate the efficacy of specific forms of treatment have been frustrated because multiple treatments are usually used in individual patients, intermediate measures of responses such as changes in clinical or laboratory variables are not always a reliable guide to survival, and no single therapy is uniformly successful.

To overcome the bias inherent in anecdotal reports of treatment successes, a registry of cases of patients with TTP was established (1). Analysis of these cases showed statistically significant trends for a beneficial effect of platelet-inhibitory drugs including both aspirin and dipyridamole (especially when used in combination) and plasma manipulation. Based on all available data, the survival rate without the above treatments is only 20% to 30%, but with them approaches 60% (1).

When viewed in the light of these findings, the recommendations for treating patients with TTP made by Rosove and associates (2) are based on erroneous conclusions. They found that nine of 14 patients treated with aspirin and dipyridamole (among other therapies) survived and interpreted this observed survival rate of 64% as evidence for a lack of effectiveness of these drugs. The correct conclusion should clearly have been the opposite since this survival rate is far better than would have been expected without such treatment, despite the (unproven) possibility that these drugs might "increase the risk of serious bleeding complications." This misinterpretation is based on their disregard not only for available evidence but also for the findings in their own series, in which only 40% of patients who did not receive aspirin and dipyridamole survived even though some were treated with plasma manipulation. Rosove and colleagues (2) submit that glucocorticoids afford the "most reasonable therapeutic approach" although there is no solid evidence for their efficacy (1). In fact, in the study they cited (their reference 21), the response to steroids alone was about 11% and the conclusion reached was that "the impact of steroids alone appears to be minimal." This is not to say that steroids should be withheld but simply further shows the distorted view presented by Rosove and colleagues.

Clearly, much progress remains to be made in treating patients with TTP. Our best evidence, however, shows that platelet-inhibitory drugs, including aspirin and dipyridamole, are indeed helpful (1). Although these drugs probably do not counteract causative factors in the pathogenesis of TTP, they are given in an attempt to interrupt the intravascular platelet aggregation that leads to fatal disseminated vascular occlusion. Therefore, the recommendations of Rosove and associates (2) would seem to represent a step backward in this unfortunate disease in which progress has been painfully slow but apparently, nonetheless, real.

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TO THE EDITOR: In their study on the use of aspirin and dipyridamole in patients with thrombotic thrombocytopenic purpura (TTP), Rosove and colleagues (1) make several assumptions that do not appear to be totally warranted from the data. They state that two of the four patients treated only with glucocorticoids died, a mortality rate of 50%. Yet they feel that "glucocorticoids should be given as soon as the diagnosis is made." I would not normally argue with this suggestion, as the mortality rate from acute TTP is much higher than 50%, were it not that this same 50% mortality rate in their aspirin-dipyridamole group constitutes the authors' reasons for negating the value of aspirin and dipyridamole. Similarly, five of 12 patients treated with plasmapheresis died, a mortality rate of 42%, which given the small study number is not significantly different from the above figures. Indeed, the one patient treated with plasmapheresis alone died. Yet plasmapheresis "should be started immediately" in the view of Rosove and associates. A time delay in clinical response does not necessarily argue for any of the above therapies because all should be effective when therapy is started. Yet we all realize that pneumonias do not disappear the minute adequate blood levels of antibiotics are reached. Subclinical improvement becomes clinical improvement gradually.

I am not arguing for the use of aspirin or dipyridamole in treating patients with TTP. Several articles discuss their beneficial use (2-4). I do think, however, that the data presented by Rosove and colleagues (1) are not sufficient for the assumptions made and that, until further studies are done, the question of aspirin and dipyridamole in treating patients with TTP is still very much unresolved.

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TO THE EDITOR: The recent article by Rosove and associates (1) adds to the morass of anecdotal literature on suggested therapies for patients with thrombotic thrombocytopenic purpura (TTP). That their patients did not markedly improve within the 2 hour onset of antiplatelet activity of the listed agents is unfortunate, but asserting that this finding argues against the efficacy of these agents is ludicrous. Improvement of end-organ disease manifestations may take several days to become clinically evident. The argument that transient clinical worsening continued on antiplatelet agents is equally fallacious, because without antiplatelet therapy deterioration may have been even more rapid. The lack of relapse after antiplatelet drug withdrawal would be expected in patients with a self-limited condition, whether or not antiplatelet drugs are of benefit during the acute phases of illness.

Curiously, Rosove and colleagues did not also argue against the

use of plasmapheresis or plasma exchange in patients with TTP although the conditions of patients in 18 of 22 courses ultimately did not improve or worsened, albeit sometimes after transient improvement. Should treatment with an 18% lasting improvement rate be considered recommended therapy?

Anecdote may be analyzed in mischievous ways, both by authors and by letter-writing critics. The article by Rosove and colleagues no more disproves the efficacy of antiplatelet agents than it disproves the efficacy of plasmapheresis or plasma exchange. Although combined therapies according to many reports have achieved moderate success in patients with this condition, we know little more conclusively about which therapies work than Moschcowitz did in 1925 (2).

Ignorance is not bliss, but let us not carve it in stone.

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In comment: To compare survival in treatment subgroups in the absence of a randomized, controlled therapeutic trial requires groups sufficiently large and demonstrably similar. Because neither our data nor anyone else's have fulfilled these requirements, we have not used survival rates as a measure of relative efficacy of treatments. The 64% survival rate of our patients treated with aspirin-dipyridamole (nine of 14) cannot be compared to the 40% survival rate in untreated patients (two of five), as Zacharski has done. The numbers of patients are too few (11 of 14 of the former, but only one of five of the latter received plasma procedures), and patients presented over a long time (8 years). The survival rate of only four patients who received glucocorticoid alone should not be used as a basis for statistical comparisons, as Billett has attempted to do.

For similar reasons, survival results from Zacharski's disease registry cannot be interpreted. Forty-eight patients from 37 institutions in 21 states were registered over 11 years. Reporting biases were undoubtedly present. Combined therapies and improved critical care medicine in recent years make unclear what helped the patients. Even then, a significantly improved survival rate was reported only for a small subset of nine patients who received specifically aspirin, dipyridamole, and sulfinpyrazone (and not in others when dextran was substituted for sulfinpyrazone). The one significant finding may well have been coincidental. Reports cited by Billett assessing the role of platelet inhibitor drugs must similarly be viewed with skepticism because treatment regimens and clinical courses often differed markedly.

To avoid these problems in interpreting survival data, we instead examined how important disease manifestations changed during treatment with aspirin-dipyridamole. We reasoned that there should be some evidence of improvement reasonably soon after therapy is begun, because the onset of drug antiplatelet action is prompt. We did not require improvement at 2 hours as proof of response and agree with Mitnick that it may take time for end-organ manifestations to improve. However, major, quantifiable disease manifestations worsened markedly during continuous treatment in 13 of 14 patients, and did not improve for 5 days in the remaining one. That aspirin-dipyridamole might prevent more rapid deterioration is extremely difficult to prove. Because benefit appears marginal at best, it is important to recognize the danger in platelet-function inhibition in severely thrombocytopenic patients. Serious bleeding complications occurred in five of our 19 patients only during platelet-inhibitor treatment. Our opinion is that these drugs should not be administered except perhaps in the context of a controlled therapeutic trial.

We were careful not to conclude that plasma procedures cure patients. Thus, Mitnick's concept of "lasting improvement" has unclear meaning. Plasma procedures appear to ameliorate temporarily the course in some patients. Perhaps improvement increases survival chances until disease remits, although there is no proof of this point.

Although we agree with Zacharski that the overall response rate to glucocorticoid appears low, we believe that there may be a responsive subset. The syndrome proved to be the initial manifestation of lupus erythematosus in one of our patients who had immediate complete remission with glucocorticoid alone. Since submission of our manuscript, another patient (Patient 1) has developed lupus erythematosus. Six of our patients had serologic abnormalities such as biologic false-positive serum VDRL, antinuclear antibodies, or hypocomplementemia. Nine of 18 of Zacharski's patients had elevated antinuclear antibodies. An array of abnormal immunologic phenomena described has been summarized elsewhere (1). We may not know at presentation which patient might have a condition overlapping lupus erythematosus, for whom glucocorticoid treatment may be necessary. Means to identify a glucocorticoid-responsive subset of patients would be of obvious value. Meanwhile, we feel that treatment is generally advisable.

Controversies over treatment have now been prevailing for years. The time has arrived for investigators interested in thrombotic thrombocytopenic purpura to band together for multi-institutional, prospective, controlled therapeutic trials. Little else will any longer suffice.

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REFERENCE

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The letters below were not forwarded to Rosove and colleagues for comment—The Editor.

TO THE EDITOR: Rosove and colleagues (1) found aspirin and dipyridamole to be ineffective in the treatment of thrombotic thrombocytopenic purpura. They used aspirin to inhibit platelet aggregation but the doses of aspirin, 0.9 to 2.7 g/d, may have been too large.

Aspirin inhibits platelet aggregation by blocking cyclooxygenase. Vascular endothelial cells synthesize prostacyclin, a substance that causes vasodilation and strong inhibition of platelet aggregation. Because the production of prostacyclin is also cyclooxygenase-dependent, the dosage and frequency of administration of aspirin are critical in determining the effect of the drug on hemostasis. The ideal regimen would block platelet aggregation without affecting prostacyclin.

It has been known for years that single, small doses of aspirin may inhibit platelet aggregation for days (2). Aspirin acetylates platelet cyclooxygenase and, because platelets make little protein, this enzyme is inactivated for the life of the platelet (about 8 days). Burch and associates (3) have shown that, in humans, a single 325-mg aspirin tablet inactivated 89% of platelet cyclooxygenase and that this inhibition only began to be relieved after 48 hours, when newly formed platelets appeared in the circulation.

In contrast to platelets, endothelial cells can make much protein, and they begin to recover the ability to make prostacyclin shortly after aspirin is gone from the circulation. Masotti and associates (4) measured prostacyclin production by the blood vessel wall in

humans after various doses of aspirin. A dose of 5 mg/kg body weight inhibited prostacyclin production by 51% after 2 hours and production returned to normal by 24 hours. A dose of 8 mg/kg body weight produced an inhibition of 90% by 2 hours. In three of nine subjects treated with 8 and 10 mg/kg body weight, the prostacyclin was still inhibited 65.8% to 81.7% at 24 hours. The doses of aspirin used in the study of Rosove and associates, 0.9 to 2.7 g/d, are likely to substantially inhibit prostacyclin synthesis throughout most of the 24 hours. These authors have shown that high doses of aspirin that inhibit platelet aggregation and prostacyclin synthesis are ineffective in thrombotic thrombocytopenic purpura and may increase the risk of serious bleeding.

A regimen of one 325-mg aspirin tablet every 2 to 3 days may be worth a trial in this disease; it would effectively inhibit platelet aggregation, have only mild and transient effects on prostacyclin synthesis, and would be less likely to cause gastrointestinal bleeding. If prostacyclin synthesis is not normally decreased in this disease, the relative lack of prostacyclin inhibition associated with this regimen may potentiate the effect of aspirin on platelet aggregation, for prostacyclin is the most potent inhibitor of platelet aggregation known.

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TO THE EDITOR: The recent article by Rosove and associates (1) implied that dipyridamole contributed to the risk of serious bleeding complications in five of 14 patients with thrombotic thrombocytopenic purpura (TTP) who had received aspirin concurrently. Numerous studies have shown that dipyridamole does not lengthen the bleeding time (2-4). Further, serious bleeding complications related directly to dipyridamole therapy without complicating clinical conditions or concurrent drug therapy have not been reported to my knowledge. Certainly, aspirin therapy has been linked to bleeding complications especially involving the gastrointestinal tract. Unfortunately, the article by Rosove and colleagues unfairly implicates dipyridamole as contributing to major hemorrhage in patients with TTP without adequate clinical proof provided.

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Hodgkin's Disease and the Pregnant Patient

TO THE EDITOR: In the December 1981 issue Jacobs and colleagues (1), with somewhat faulty logic, discuss the management of pregnant patients with Hodgkin's disease. They recommend local radiation in inadequately staged women. A good rule in planning curative cancer therapy is to treat local disease with local therapy (surgery or radiation); treat systemic disease with systemic therapy (drugs). Application of this rule led to the successful practice of staging and treating patients with Hodgkin's disease.

But in the pregnant woman adequate staging is proscribed. She is, by necessity, understaged. When laparotomy is omitted there is a 30% chance of understaging; the chance of understaging is even greater when the standard radiologic studies are omitted as well. In these patients radiation, striking only perceived disease, will be inadequate. Chemotherapy striking all disease areas is the preferred treatment.

Jacobs and associates (1) recommend radiation during pregnancy despite the established risks of fetal exposure during all trimesters (2). They quote predicted doses for the fetus during maternal radiation above the diaphragm, showing that it is not possible to administer conventional curative doses of radiation for the pregnant women with Hodgkin's disease and avoid internal scatter to the fetus. The more advanced the pregnancy, the higher is the fundus, and the greater is the dose from scatter. No dose of radiation to the fetus is completely safe (2).

On the other hand, there is a gratifying lack of data incriminating chemotherapy as teratogenic. Except for antimetabolites, chemotherapeutic drugs, *used without concomitant radiation,* have not been associated with significant increase in fetal abnormalities during the first trimester; infants, exposed from the second trimester on, appear to be virtually free of abnormalities.

Their Table 2 is an inadequate summary of the experience with chemotherapy. References with useful data are omitted (3-5, for example). Even data from their own experience (1) and from their cited references are not included (their references 13, 14). Some cases offered as examples of the teratogenicity of chemotherapy had, in fact, also included radiation (their references 16, 17).

They recommend suboptimal radiation or sub-suboptimal single-agent chemotherapy in young women with Hodgkin's disease, a curable malignancy. The practice of irradiating "involved fields" to a suboptimal 2000 rad in inadequately staged patients is not sound. Undiscovered and untreated abdominal disease could lead to advancement of disease while "stabilization of disease" above the diaphragm is underway. When disease requiring new treatment fields is discovered at staging after delivery, the therapist risks administering excessive radiation at the treatment field junctions. When systemic disease requiring chemotherapy is discovered, the patient is exposed to an increased risk of acute leukemia due to the combined radiation and chemotherapy. When the mother has systemic symptoms "so severe that they may be detrimental," she needs effective systemic chemotherapy (nitrogen mustard, vincristine, procarbazine, prednisone), not "involved field" radiation or single-agent chemotherapy.

Jacobs and associates acknowledge that the known risks of radiation of the fetus outweigh any demonstrable risk to the fetus from chemotherapy. Their selection of radiation as the preferred treatment is a dichotomy. Reflecting on the risks of radiation they recommend abortion during the first 20 weeks of pregnancy. Because chemotherapy is safe in early pregnancy, certainly after 10 weeks, this fetal wastage can be avoided.

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In response: Responding to each of the multiple criticisms of Chapman and Crosby is difficult. We certainly understand, in fact have helped establish, the principles of the proper management of patients with Hodgkin's disease. We believe our article adequately explains our reasoning. Chapman and Crosby have a right to disagree, and the reader must decide whose advice and experience to accept.

Chapman and Crosby appropriately call to our attention several recorded experiences with successful pregnancy during combination chemotherapy of the mechlorethamine hydrochloride, vincristine, procarbazine, and prednisone (MOPP)-type. Two of these were published after our manuscript was prepared. Even these several reports, however, do not justify the use of MOPP-like therapy during pregnancy versus the appropriate use of limited irradiation in the second or third trimester. How can Chapman and Crosby accept that "no dose of radiation to the fetus is completely safe" and imply that MOPP chemotherapy is safe, based on such limited experience and follow-up?

We believe our recommendations are sound and our final paragraph still relevant: "These are only . . . guidelines. Each case must be individualized. . . . Because of the high potential for cure, the pregnant patient with Hodgkin's disease should be managed in a manner that is optimal for the health of the mother and infant." In a rare woman, MOPP chemotherapy will be required; for most of them definitive staging and chemotherapy can be safely delayed.

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Hodgkin's Disease, Hypothyroidism, and Hyperthermia

TO THE EDITOR: We report the case of a ritualistic jogger who developed hyperthermia while jogging 8 months after she was found to have Hodgkin's disease.

A 39-year-old white woman presented with an enlarged left cervical lymph node and was found, after exploratory laparotomy and splenectomy in April 1980, to have Hodgkin's disease, nodular sclerosis type, stage II A. She was subsequently treated with mantle radiation (total, 4000 rad). Her medical history included hyperthyroidism treated initially with propylthiouracil and then by subtotal thyroidectomy in 1974. After radiation therapy for the Hodgkin's disease was completed, the patient developed hypothyroidism, which was corrected with thyroid hormone supplements.

In December 1980 she began to complain of chills and fever (temperatures up to 38.9 to 39.4° C) occurring during her jogging but completely subsiding approximately 1 hour and 45 minutes after she finished jogging. The patient had never had similar symptoms. She is otherwise asymptomatic, with normal resting temperatures on numerous measurements by herself and by us.

Her disease remains in complete remission after a recent evaluation in November 1981 when a persistent parapneumonic effusion that followed lobar pneumonia was drained, and open-lung and pleural biopsies were negative for Hodgkin's disease.

Although hyperthermia has been reported in marathon runners (1), we have been unable to find any report of hyperthermia induced by exercise, such as jogging, in patients with Hodgkin's disease. Interestingly, although our patient has remained in complete remission 22 months after radiation therapy she experienced unexplained chills and fever for 7 months when jogging. We are uncertain about the nature of this phenomenon and whether it is causally related to Hodgkin's disease. Persistent hyperthermia has been described as a symptom in splenectomized patients, particularly those with hematologic disorders and hypersplenism (2), but no association with exercise has been documented. We are interested in hearing from physicians treating patients with Hodgkin's disease or any other lymphoproliferative disorder, who have seen a similar phenomenon.

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Replacement Doses of Levothyroxine

TO THE EDITOR: We read with interest the article by Rosenbaum and Barzel on levothyroxine replacement doses for primary hypothyroidism (1). Although their data emphasize quite rightly the need for reliable indices for correctly adjusting long-standing hormone replacement doses, they also raise several questions.

First, the highest levothyroxine doses required (shown in their Figure 1) were given to two young subjects, 15 and 30 years of age. Were these two patients the ones with congenital hypothyroidism? If this were so, we would recommend caution in the interpretation of basal thyrotropin levels in such patients because follow-up data of patients with congenital hypothyroidism have shown that thyrotropin levels could remain supranormal for several months after correction of hypothyroidism. So far an explanation for this anomaly has not been found in the feedback mechanisms. It is assumed that some definitive modification at the pituitary level occurs, which could then lead to over-estimation of the replacement doses (2, 3).

Second, the authors also indicate that changes in replacement doses were based on total thyroxine levels. Therefore, the adjustment does not take into account the known variations of the thyroxine-binding proteins and specifically those of thyroxine-binding globulin in the normal population an in persons with hypothyroidism (4, 5). The weak statistical correlation calculated by Rosenbaum and Barzel and shown in their Figure 1 would be valid only if calculated on a free thyroxine index or a thyroxine-to-thyroxine-binding-blobulin ratio, rather than total thyroxine levels.

Third, Rosenbaum and Barzel indicate that the changes in replacement doses were also based on thyrotropin levels. We reported last year (6) that basal thyrotropin levels were increasing progressively with aging in a normal population of 250 subjects (from 2 to 91 years old) independently of total thyroxine and the presence of autoimmune thyroiditis. Our findings suggest that the setting of the pituitary thyrostat could be modified in the elderly (perhaps in relation to changes in the peripheral metabolism of thyroid hormones) and, therefore, cast some doubt on the use of

slightly elevated thyrotropin levels as an index for the adjustment of thyroxine doses for patients above 65 years of age.

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In response: The intriguing fact of abnormal behavior of serum thyrotropin in patients with congenital hypothyroidism does not apply to our cases (1). Our two patients with congenital hypothyroidism have been on replacement therapy for years. Their levothyroxine requirement, 150 and 100 μg/d, was determined when their treatment was changed from dessicated thyroid to this medication. The highest daily levothyroxine doses, 400 and 300 μg, were being taken by the heaviest men in our study, a 25-year-old man weighing 139 kg and a 30-year-old man weighing 114 kg, respectively.

Our study reports an average dose required in a population of patients whose average thyroxine-binding globulin at the time of full replacement was within the normal limits, except as noted in our Table 1. In any event, the absolute thyroxine turnover (micrograms per day) remains unchanged even when changes in thyroid hormone binding lead to alteration in the fractional clearance and total serum thyroxine level (2). It is the absolute amount turned over that is being replaced by the daily maintenance dose of levothyroxine. The correlation between age and dose is significant at $p < 0.0001$, which means that there is only a one in 10 000 chance that this correlation is accidental. Further manipulation of the data could possibly have produced a somewhat tighter statistical fit, but inasmuch as age is only one determinant of the final dose (*see* our Table 2), a perfect correlation cannot be expected.

The upward adjustment, and especially the final upward adjustment, of the thyroxine replacement dose was based in every case primarily on serum thyrotropin levels. Clinically, full replacement has been achieved in all cases. This result and the fact that the final serum thyroxine and thyrotropin levels were virtually identical in the older and younger patient groups shows that the thyrotropin blood level is indeed an excellent clinical guage for titrating the dose required by any hypothyroid patient. This therapeutic approach is especially useful in the management of aged patients who are most likely to suffer untoward results from overtreatment.

Little is known about the thyroid-pituitary-hypothalamic axis in the aged. For this reason, we have studied the effect of thyrotropin-releasing hormone on thyrotropin release after small decreases in serum thyroid hormone concentrations in elderly patients. In our study (3), which is being presented at the forthcoming meeting of the American Association of Physicians, we show that basal thyrotropin was normal in 24 ambulatory subjects between 64 and 87 years of age. However, the thyrotropin response to thyrotropin-releasing hormone after small decrease in serum thyroxine levels in some of these clinically euthyroid patients was subnormal based on criteria established in young subjects. The clinical significance of our observation is that the degree of thyrotropin elevation seen in elderly patients with hypothyroidism may be less than expected, but this finding does not negate the utility of thyrotropin measurement in treating patients with hypothyroidism or the failing thyroid gland syndrome (4).

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Medical Treatment of Primary Hyperparathyroidism

TO THE EDITOR: I enjoyed Bilezikian's timely and well-thought-out article on the medical management of primary hyperparathyroidism (1). However, in regard to his remarks on cimetidine and propranolol administration to suppress parathyroid hormone secretion, I believe he is unnecessarily restrained. In my view, there is no reliable evidence to support the use of either agent. More importantly, Rudnick and colleages (2) point out in the same issue that cimetidine can occasionally induce disastrous renal failure. Cimetidine may also impair renal tubular secretion of creatinine (3); in treating normal volunteers and patients with primary and secondary hyperparathyroidism, we found significant increases of serum creatinine levels (4, 5). Especially in persons with renal insufficiency, such effects of cimetidine on creatinine are confusing and troublesome at best. Because there are no reliable data to support the use of propranolol or cimetidine in patients with primary hyperparathyroidism and because the drugs are not completely harmless, physicians would be well advised to avoid their use solely for the hope of improving the signs and symptoms of hypercalcemia.

Bilezekian's advice is wise: for those truly asymptomatic patients with mild hyperparathyroidism not treated surgically, there should be regular and careful observation for complications. In these patients, "medical therapy" is costly, ineffective, and potentially dangerous.

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Cimetidine-Theophylline Interaction

To the editor: Recent reports have shown that cimetidine decreases theophylline clearance (1-3), and it is suggested that the decrease is caused by an inhibition of hepatic metabolism by cimetidine or its metabolites (2, 4). We report two cases that provide additional information on the reversibility and potential mechanism of this drug interaction.

Patient 1: A 50-year-old black woman with a severe asthma attack was admitted to the medicine service on 1 July 1981. She had been discharged from the hospital on 25 June after treatment for upper gastrointestinal bleeding, for which cimetidine, 300 mg orally four times a day, had been started on 24 June. At that time her steady-state theophylline level was 4.2 μg/mL on a continous intravenous infusion of aminophylline, 20 mg/h. After admission on 1 July cimetidine treatment continued and the aminophylline regimen was changed from oral administration to continuous infusion, 30 mg/h. Methylprednisolone, 60 mg intravenously every 6 h; tetracycline hydrochloride, 500 mg orally every 6 h, Maalox (William H. Rorer, Inc., Fort Washington, Pennsylvania), 30 mL orally every 6 h; and ferrous sulfate, 300 mg orally three times a day, were ordered also. On 2 July 1981 a theophylline level of 25.7 μg/mL was obtained.

Patient 2: A 62-year-old white woman was admitted on 9 July 1981. When she had been admitted earlier, on 5 June 1981, cimetidine, 300 mg orally every 6 h, had been begun for what was thought to be an active ulcer. At her nursing home aminophylline therapy, 200 mg orally every 6 h, was also started for shortness of breath. Her current medication regimen included: neomycin, 500 mg orally every 6 h; spironolactone (Aldactone, Searle Laboratories, Chicago, Illinois), 25 mg orally three times a day; digoxin, 0.125 mg orally every day; ampicillin, 1 g intravenously every 6 h; and tobramycin, 65 mg intravenously every 48 h. On 11 July 1981 aminophylline therapy was discontinued when the blood level from the previous day was found to be 41.2 μg/mL. Cimetidine was discontinued on 15 July at 2200 h. She became unresponsive and gradually lapsed into hepatic coma and died on 1 August after liver failure.

In both patients cimetidine apparently reduced the rate of metabolism of aminophylline. This effect was present with normal hepatic function (Patient 1) and in severe hepatic disease (Patient 2). In Patient 1 theophylline clearance was 4.75 L/h before and 1.17 L/h during cimetidine treatment. Under the assumption of unchanged volume of distribution of 0.45 L/kg, the theophylline half-life increased from 2.7 h to 7.8 h. From the theophylline concentration-time data of Patient 2, the elimination rate constant after termination of theophylline dosing was calculated by regression analysis assuming a one-compartment model. The elimination rate constant during cimetidine therapy was 0.00583 L/h ($r = 0.978$, $n = 3$) but after discontinuation it was 0.01063 L/h ($r = 0.9947$, $n = 3$). This change corresponds to a theophylline half-life of 118.9 h with cimetidine and 65.2 h after discontinuation. In Patient 2 with end-stage liver disease and a tremendously long theophylline half-life, termination of cimetidine treatment resulted in a rapid lowering of the theophylline half-life. The rapid decrease and the fact that cimetidine is not extensively metabolized suggest that cimetidine binds to the enzyme systems (affinity) that metabolize theophylline without actually interfering with the intrinsic activity. It is also possible that the cimetidine-theophylline interaction does not occur in the liver, but that theophylline forms a complex with cimetidine in the blood, thus preventing theophylline from being metabolized (5). Cimetidine is not extensively metabolized but binds to the cytochrome p450 system with a type II spectial change (4). Thus, we agree with the conclusions of Reitberg and colleages (3) that this interaction requires further study.

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Disopyramide and Bundle-Branch Block

To the editor: The article on disopyramide (1) is a comprehensive and stimulating statement. A case we have recently reported elsewhere (2) suggests, however, that disopyramide may not be safe for use in the presence of bundle-branch block. A 57-year-old woman with right bundle branch block and left posterior hemiblock and ventricular premature contractions subsequently developed heart block after administration of disopyramide phosphate (Norpace, Searle Laboratories, Chicago, Illinois). With a drug challenge after implantation of a permanent pacemaker, the patient developed intermittent complete heart block.

On the basis of this isolated case, close monitoring of disopyramide-treated patients who have atrioventricular or intraventricular conduction abnormalities appears to be appropriate.

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Naloxone, Beta Endorphins, and High-Altitude Pulmonary Edema

To the editor: High-altitude pulmonary edema develops in certain unacclimatized and susceptible persons acutely exposed to extreme elevation. Since its original report the clinical manifestations have been well described, but despite numerous speculations the pathogenesis of this disorder remains unclear (1-3).

We describe here an otherwise healthy man who presented with high-altitude pulmonary edema, in whom plasma beta endorphins were measured and found to be significantly elevated. Dramatic improvement in the patient's hypoxemia and clinical course occurred after administration of naloxone. We postulate that this opiate antagonist may be beneficial in the treatment of this disorder.

A 22-year-old white man, who had dyspnea, headache, nausea, and cough productive of frothy sputum for 12 hours, was transported by

helicopter to the St. Anthony's Hospital emergency department (altitude, 1676 metres). A resident of Colorado Springs, Colorado (altitude, 1859 metres), the patient had spent the 3 days before admission mountain climbing at 3505 metres in the Rocky Mountain Range. His medical history was unremarkable for cardiopulmonary disease. On arrival to the emergency department, the patient was diaphoretic and in respiratory distress with a systemic blood pressure of 100/70 mm Hg; pulse, 130 beats/min; respiratory rate, 36/min, and temperature, 37.2 °C. The perioral area and distal extremities were cyanotic. No retinal hemorrhages were seen. Moist rales were heard two thirds the distance up from both lung bases. There was no jugular venous distension. Cardiac examination showed no murmurs or extra heart sound. One hundred percent oxygen was administered through a non-rebreathing mask at 5 L/min without clinical changes. The arterial blood gases on the mask showed pH, 7.34; Po_2, 55 mm Hg; Pco_2, 21 mm Hg; and oxygen saturation, 85%. A chest film showed bilateral diffuse patchy alveolar infiltrates with normal cardiac silhouette. Electrolytes and blood area nitrogen and blood glucose levels were normal. Blood and urine drug screens showed negative findings. Plasma obtained from the patient and a normal control subject were assayed for beta endorphins, which measures 250 and 45 pg/mL respectively (New England Nuclear Radioimmunoassay Kit, Boston, Massachusetts).

Naloxone, 1.6 mg, was administered intravenously. Within 15 minutes, the patient's symptoms had improved, with a reduction in heart rate to 80 beats/min and respiratory rate to 26/min. Arterial blood gases with the same fractional oxygen concentration showed dramatic improvement with pH, 7.42; Po_2, 132 mm Hg; Pco_2, 26 mm Hg; and oxygen saturation, 98%. Other than oxygen and naloxone, no medications were administered. One hour after naloxone administration, the patient became tachypneic (respiratory rate, 30), tachycardiac (heart rate, 106), and dyspneic with arterial blood gases measuring pH, 7.37; Po_2, 62 mm Hg; Pco_2, 23 mm Hg; and oxygen saturation, 89%. Naloxone, 0.8 mg, was administered intravenously and resolution of the patient's symptoms occurred within 10 minutes. After 20 minutes arterial blood gases measured pH, 7.44; Po_2, 102 mm Hg; Pco_2, 33 mm Hg; and oxygen saturation, 97%. The patient continued to improve and was discharged on the third hospital day with normal findings on chest roentgenogram and normal room air arterial blood gases.

Naloxone, a specific opiate antagonist, is thought to inhibit endorphin binding to opiate receptors, although the precise mechanism and kinetics are not clearly defined. A role of endorphins and naloxone in the pathogenesis and treatment of patients with high-altitude pulmonary edema has not been previously postulated. Treatment consists of rapid descent to normal altitude, oxygen administration, and bedrest. Pharmacologic agents used in cardiogenic pulmonary edema have been found ineffective and may be contraindicated (4). Findings in this case suggest that high-altitude pulmonary edema may be mediated in part by endorphinergic mechanisms and that naloxone, through its antagonist effects, may help block these. Further studies are needed to define naloxone's potential as a preventive and therapeutic agent in high-altitude pulmonary edema.

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Correction: Editorial Note on Atenolol

The title of an editorial note in our February issue (1) should have read, "Atenolol: A Long-Acting $Beta_1$-Adrenoceptor Antagonist" (not antenolol).

REFERENCE

1. MCLEOD AA, SHAND DG. Atenolol: a long-acting $beta_1$-adrenoceptor antagonist. *Ann Intern Med.* 1982;**96**:244-5. Editorial note.

Correction: Letter on HLA-B27 Testing

A letter in our March issue (1) comments on an article by Khan and Khan, not Kahn and Kahn as misspelled in both the letter and reference.

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1. MERZ D. Non-utility of the HLA-B27 test. *Ann Intern Med.* 1982; **96**:383-4. Letter.