Refer to: Migraine—Medical Staff Conference, University of California, San Francisco. West J Med 123:211-217, Sep 1975

Medical Staff Conference

Migraine

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The first topic for presentation at Medical Grand Rounds today will be that of current concepts of migraine. We are very pleased to have Dr. Neil Raskin, Associate Professor of Neurology. Dr. Raskin will present a patient to us this morning and discuss this important topic.*

DR. RASKIN:† Thank you, Dr. Smith. Mr. S. has kindly consented to share his morning with us today. He has a rather interesting and unusual headache problem that I will have him tell you about. Although it is uncommon, it illustrates several pertinent points regarding the nature and mechanism of migrainous disorders. Mr. S. is now 64 years of age, and until five years ago only rarely experienced a mild headache. No one in his family has experienced headache, nor are there any circumstances that he can recall that have ever provoked headache.

Five years ago a cholecystectomy was carried out because of asymptomatic gallstones. After the patient ate his first postoperative meal, he experienced an extraordinary headache that persisted for about a day. Ever since then he has experienced headache upon the ingestion of certain foods; and I should like him to tell you about the foods that can do this and how soon after their ingestion he experiences headaches.

MR. S.: *It took quite a bit of analysis on my part to find out what foods actually did cause my headaches, and through elimination of certain foods from my diet, which took quite some time, I found that foods which contained a high degree of fat cooked at a high temperature or fried foods would induce a headache.*

DR. RASKIN: How long after eating these foods did you experience headache?

Patient: The headaches would start about an hour after eating fatty foods, and would last a minimum of 24 hours, depending on the amount of food.

DR. RASKIN: Other than fatty foods, there have been other foods that you discovered would cause headache; chocolate is one of them, is that correct?

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Neil H. Raskin, MD, Associate Professor of Neurology.

Patient: Chocolate used to cause headache, but I now take chocolate in moderation. Pressurized, oil-containing food, such as tuna or salmon, will give me a very severe headache. Soy sauce, frankfurters and bacon are also avoided.

DR. RASKIN: Did you ever go on a fruit diet to reduce your headache frequency?

Patient: Yes, it worked. However, while eating more fruits I would also watch my consumption of meats and how they were prepared.

DR. RASKIN: Where is your headache located?

Patient: The front bilaterally.

DR. RASKIN: Did your face ever discolor when you experienced headache, and is the nature of your headache ever pulsatile or is it a deep dull pain?

Patient: It is deep and dull, and with severe headaches the pain would seem to concentrate behind the eye: it felt in some cases like the eyeball was going to come out. My family tells me that my face is flushed when I have my headaches.

DR. RASKIN: Was it always the left eye or is it ever on the right side?

Patient: It is more concentrated on the left side.

DR. RASKIN: Do you ever see light flashes or sparkles or any other bright sensations with headache?

Patient: No.

DR. RASKIN: There have not been any other migrainous features to the patient's headache. Findings on skull and sinus x-ray studies were normal and several antihistamine preparations had been tried before my seeing him about a year ago. Upon the institution of ergonovine maleate, would you tell us what happened to your headache problem?

Patient: At first I took two tablets after each meal, morning, noon and night, and the headaches disappeared. Then gradually I reduced the number of tablets to two a day, two after the evening meal before I retired.

DR. RASKIN: Do you now have headache at all?

Patient: No, if I follow that procedure, no headaches.

DR. RASKIN: How many times during this past year have you gone off the pills?

Patient: A dozen or more for short durations.

TABLE 1.—*Foods Considered to be Migraine Precipitants and Excluded from the Diet of 240 Patients*

Food	*Number of Patients*	*Percent*
Chocolate	175	73
Dairy products (cheese)	114	48
Fruits (citrus)	80	30
Alcohol	60	25
Fatty fried food	45	19
Vegetables (onions)	42	18
Meat (pork)	35	15
Tea and coffee	35	15
Seafood	24	10

DR. RASKIN: What happened?

Patient: The headaches returned each time.

QUESTION: Does alcohol provoke his headaches?

Patient: No.

DR. RASKIN: Thank you very much, Mr. S., for spending this morning with us.

In summary, Mr. S., who is now 64, developed at the age of 60 a headache pattern that is rather nondescript; it is bifrontal and sometimes retroorbital in location, nonpulsatile and not associated with a characteristic aura. It was often severe pain. It appears to be controlled by the ingestion of an ergot alkaloid. Is this disorder migraine? I think so. Responsiveness to an ergot alkaloid is, in my view, the most useful definition of migraine presently available.

Mr. S.'s disorder is illustrative of the most interesting and exciting development in migraine research, something that has come to be known as "dietary migraine." Several years ago, a group in England headed by Edda Hanington[1] put together the data shown in Table 1 which were derived from a large number of patients with migraine. This is a group of food items that can provoke headache in certain susceptible patients who also have spontaneously occurring vascular headaches (migraine). Chocolate heads the list, followed by cheese, fruits, alcohol, fried foods and others. They compared this food group with another assortment of foods that were known to provoke headaches and hypertension in patients who had been taking monoamine oxidase (MAO) inhibitors. Cheese was the food most often incriminated, but other foods were implicated as well; the similarity between these two food groups is notable.

One of the offending chemical agents in these foods is tryamine, which liberates excessive norepinephrine from nerve endings if its degradative

pathway is blocked by an MAO inhibitor, producing acute elevations in blood pressure and headache. New York State cheddars are quite high in tyramine concentration, and chianti is higher than other wines (Table 2).[2] This correlates with some reports that chianti, more frequently than other red wine, triggers off headache in people so disposed. But you can even have your cheese and not have headache. The tyramine content of cheese is concentrated near the rind.[3] Cheese is abundant with tyrosine, which is decarboxylated to tyramine by decarboxylase-containing bacteria which are located in the rind. Therefore, if one were so inclined, one could slice away the rind and have one's cheese without eating much tyramine.

Since migraine is probably an hereditary disorder, there may be a genetic enzyme deficiency (possibly of monoamine oxidase) in some migraine sufferers. Such a deficiency might occasionally lead to increased tissue amine levels. A possible explanation of at least some attacks of migraine may be that in certain people there is a sensitive localized vascular response to circulating amines such as tyramine. To test this possibility, experiments were devised to ascertain whether migraine attacks could be precipitated by giving patients tyramine by mouth. It is now clear that patients with food-induced vascular headaches can be identified by their sensitivity to tyramine administration. In 17 patients with dietary migraine, headaches were produced 40 times in 49 administrations of tyramine, but only twice in 26 administrations of lactose tablets.[1] Patients with recurring headache disorders, but without food sensitivity, do not respond adversely to tyramine administration. There is clearly something different about patients with dietary migraine.

TABLE 2.—*Tyramine Content of Various Foods*

Product	*Tyramine (μg/g or μg/ml)**
Cheeses	
Camembert	86
Stilton	466
Brie	180
Emmentaler	225
New York State cheddar	1,416
Gruyere	516
Processed American	50
Cream	ND†
Cottage	ND
Yeast	ND
Yogurt	ND
Beer	
Brand A	1.8
Brand B	2.3
Brand C	4.4
Wine	
Sherry	3.6
Sauterne	0.4
Riesling	0.6
Chianti	25.4
Port	ND

*Cheeses expressed in μg/g; beers and wines in μg/ml.
†ND = not detected, being <0.2 μg/gm or μg/ml.

A problem with the tyramine hypothesis arose when it was learned that chocolate, which is at the head of this list of food offenders, contained no tyramine. However, it has recently been found that chocolate contains another vasoactive monoamine, phenylethylamine.[4] Patients who experienced headache after the ingestion of chocolate were challenged with phenylethylamine and headache was provoked much more frequently than after placebo administration. This took the monoamine oxidase theory up another notch. Since there is good evidence suggesting that monoamine oxidase exists in immunologically separable forms, for one of which phenylethylamine is the preferred substrate, a possible mechanism for chocolate-induced headache is that in these people there might be a deficiency of an isoenzyme of monoamine oxidase.

This possibility was examined by assessing platelet monoamine oxidase activity with various monoamine substrates in patients with migraine, in patients with chocolate-induced headache and in control subjects. The patients with chocolate-induced headache did not show a specific deficiency in phenylethylamine-dependent monoamine oxidase activity; the hypothesis is, therefore, not supported. On the other hand, in the patients with headache, both migraine and chocolate-sensitive, there was low platelet monoamine oxidase activity (compared with the control patients) which was statistically significant (Table 3). The activity was low with all four monoamine substrates used (phenylethylamine, tyramine, dopamine and 5-hydroxytryptamine).[4] This is one of the first biochemical distinctions ever made between patients with migraine and control subjects. They are preliminary data, but they provide an important clue toward understanding the migraine mechanism. This is the current status of the dietary migraine story; patients with food-precipitated headache comprise a rather small percentage of those patients with recurring headaches,

probably no greater than 5 percent. The other 95 percent of patients is the subject of the remainder of my remarks.

How can migraine be identified? Classical migraine is difficult to miss. We have all been taught to recognize hemicranial pulsating pain which is associated with retching and preceded by sparkling zigzags in a field of vision contralateral to the hemicephalgia. However, this classical syndrome is a rather uncommon one. It is certainly distinctive, but is representative of only a small fraction of the migraine population. The important public health problem, we all agree, is what has come to be called common migraine. Unfortunately, there is no consensus regarding the criteria or even the constituents of the latter disorder. Since this is a common source of discomfort for a large number of people, it is important to arrive at an operational definition of the disorder, since many effective pharmacological agents are now available for its treatment. By way of contrast, treatment nodes for muscle-contraction, or tension headache, are rather ineffectual in my experience; I avoid such a diagnosis until it becomes unreasonable to do so any longer. The large majority of patients with occipitonuchal pain and muscle tightness also complain of headache, in another location, which usually bears the features of a vascular headache. At the head and neck, as in other parts of the body, muscle splinting in response to pain occurs. Recognizing the vascular component of these so-called mixed "tension-vascular" headaches will enable you to deal more effectively with your patients.

Let us consider the mechanisms underlying headache. Cerebral tissue is pain-insensitive; when pain is experienced about the head and neck vascular mechanisms are prominent: traction on the great venous sinuses or some of the large intracranial arteries, or dilatation of intracranial or extracranial arteries; in addition, inflammation of the meninges, or direct pressure upon the upper cervical roots are other important mechanisms. Many neurologists have come to the view that vascular mechanisms commonly underlie complaints of headache. Not all vascular headaches are migrainous; migraine is an idiopathic disorder, without underlying structural abnormalities. Lumbar puncture headaches are also vascular headaches. Headaches that occur in settings of vasculitis, as in periarteritis or lupus, are vascular headaches as well. These may be indistinguishable from what we might otherwise regard as migraine headaches. One of our jobs as physicians is to be sure that patients who present with vascular headaches, in fact, have no underlying structural cause for their complaint. In general, these causes are rather uncommon in dealing with patients with recurring episodic headaches. Harold Wolff provided the most direct evidence that the headache phase in migraine at least correlates with dilatation and stretching of arterial walls; nerve endings in these arterial walls relay this information centrally and pain is the response rendered. This is probably why the quality of pain experienced by the large majority of patients with migraine is a pulsatile, thumping or pounding sensation (throbbing).

The mechanism of the aura or of the migraine equivalents (migraine without headache) when they occur is probably through constriction of intracerebral arteries; the neurological symptoms that occur are dependent upon which part of the brain becomes ischemic. Aphasia, hemiplegia and tingling on one side of the body may occur; visual

TABLE 3.—*Human Platelet Monoamine Oxidase Activity*

Substrate	*Migraine*		*Patient Control*		*Chocolate-Sensitive Migraine*
Phenylethylamine	4.38±0.51 (28)	P<0.001	10.66±0.96 (26)	P<0.001	4.16±0.36 (12)
Tyramine	13.52±1.60 (28)	P<0.001	28.48±2.64 (26)	P<0.001	11.80±1.26 (12)
Dopamine	5.61±0.51 (28)	P<0.050	8.29±1.09 (26)	P<0.010	5.04±0.44 (12)
5-Hydroxytryptamine	14.54±1.17 (16)	P<0.010	21.70±1.82 (14)	P<0.050	15.84±1.88 (7)

P = statistically significant difference.

Each value is expressed as nanomole of substrate deaminated per 30 minute incubation per mg protein at 37°C. Protein nitrogen was measured according to the method of Lowry and co-workers[24] using human serum albumin as standard. Figures in parentheses represent number of subjects.

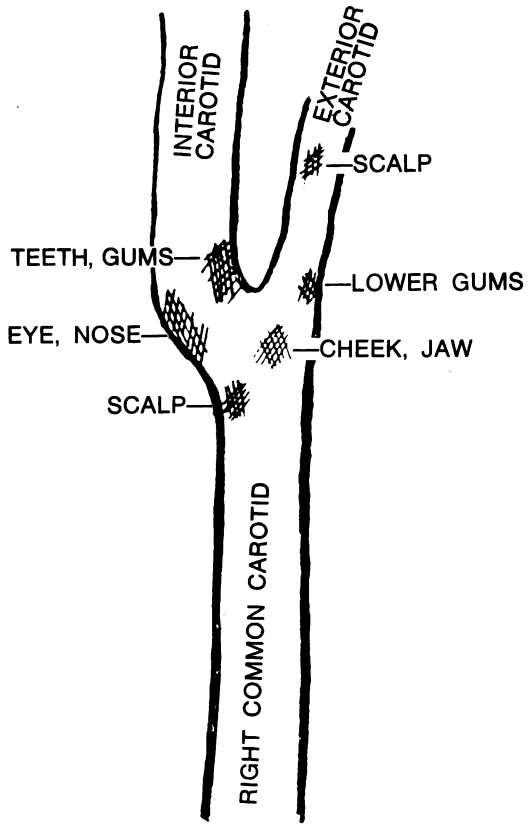

Figure 1.—Right common carotid artery and bifurcation with areas stimulated by faradic current showing reference of pain as determined by the patient during the period of stimulation. (Reproduced with permission from Ann Otol Rhinol Laryngol.[5])

symptoms are especially frequent because of the common involvement of the posterior cerebral artery in this process. Therefore, vascular headache disorders are comprised of both intracerebral vasoconstriction and extracerebral vasodilatation. Efforts at countering vasodilatation are useful therapeutically. Ice packs and the inhalation of 100 percent oxygen are helpful in general, whereas efforts that produce vasodilatation, such as heat applications or the ingestion of nitroglycerin tablets, may precipitate or exacerbate a vascular headache disorder.

It is perhaps intuitive that if one implanted electrodes in scalp arteries, pain would result in regions of the head overlying the vessel stimulated. It is not very well known that the carotid artery has special attributes. Fascinating experiments were done in the 1930's by Temple Fay[5] in Philadelphia, and reproduced by Bronson Ray in New York in the early 1940's, regarding the carotid artery wall and pain, which appear to corroborate a clinical observation that some of us have made recently. Electrodes implanted in the carotid artery near its bifurcation may produce pain over portions of the head and neck that I do not believe would have been predicted (Figure 1). Stimulation at one point produces pain in the cheek and jaw, a few millimeters away in the lower gums, another few millimeters laterally in the scalp, and so on. Carotidynia, or a painful carotid artery, is a term which has been rather vaguely used over the years. Dr. Stanley Prusiner and I have observed several patients in whom a tender carotid artery has been the apparent focus of a disorder characterized by episodic pulsatile neck or jaw pain in patients with preexisting migraine headaches.[6] This syndrome, carotidynia, has been responsive to administration of the very same drugs that alleviate migraine headaches. It is probably a migraine variant. We are now finding many patients with migraine in its many forms who have tender carotids, always ipsilateral to the episodic pain. Sometimes if the carotid artery is compressed, the patient's pain may be reproduced. This is a sign worth eliciting in a patient with a recurring pain disorder, and we believe it identifies its mechanism as migrainous.

The idea of central vasomotor instability, a putative mechanism underlying this group of disorders, is gaining support. The strongest evidence for vasomotor instability in patients with migraine stems from their responsiveness to a variety of biological stimuli. Exercise, an activity that is associated with vasodilatation of skeletal muscle arteries, sometimes causes headaches. Often these headaches are accompanied by scintillating scotomata ("sparkles"); thus, inappropriate cephalic vascular responses (vasomotor instability) to physical exertion occur in patients susceptible to migraine headaches and help us to recognize the migraine mechanism. There are other patients who, if they receive less than eight hours of sleep, awaken the next morning with headaches; others experience headache in association with menstruation, in response to flickering or bright lights, during the letdown period following stress or shortly after the drinking of an alcoholic beverage. These biological precipitants are probably more specific toward defining what migraine is than the descriptive features of classical migraine (aura, hemicranial headache, vomiting and the like). Headache that occurs an hour after only modest hunger and no clinically significant hypoglycemia is a common characteristic of migraine. People who, upon bending down for the soap in

the shower, arise quickly and experience a visual dim-out, scintillating scotomata or vertigo are more likely to experience migraine headaches.[7]

Let us return to other biological undercurrents of migraine. In the late 1950's, methysergide was brought forth for migraine prophylaxis. This agent was and is used daily to block the migraine mechanism, thus preventing headache occurrences. During the early clinical trials, it was clear that it was, indeed, effective but to the surprise of most it was found not to be a potent vasoconstrictor; in fact, there was a poor correlation between headache relief and evidence of vasoconstriction. The mechanism of action of methysergide was an open question. It was then learned that methysergide was a pharmacological antagonist of serotonin, which set off a wave of speculation that serotoninemia characterized the migraine state.[8] Against this notion was the observation that headache is not a feature of the carcinoid syndrome; furthermore, infusions of serotonin in patients with migraine alleviated their headache, presumably because of the vasoconstrictor effect of serotonin. However, urinary metabolites of serotonin were measured, and it was found that there was an excess of 5-hydroxyindoleacetic acid during the headache phase of migraine. Lance has shown that there is a 30 percent decrease in platelet serotonin during a migraine headache.[9] This is a finding that has now been reproduced by several laboratories and appears to be a consistent biological concomitant of migraine. However, further interactions of serotonin with the organism are not at all clear. No serotonin appears in cerebrospinal fluid, for example, during headache. The initial enthusiasm regarding the implication of serotonin in migraine has not met with the reward of insight. On the other hand, it has led to a group of drugs, some of which are thought to be serotonin antagonists, which are generally effective in ameliorating the migraine state.[10] Thus, it has been operationally useful to pursue the hypothesis that serotonin is somehow involved in the migraine mechanism.

TABLE 4.—*Differences Between Migraine and "Migrainous Neuralgia"*

	Migraine	*"Migrainous Neuralgia" (cluster headache)*
Frequency of attacks	<1-12/month	1-8/day
Usual duration of pain	4-24 hours	0.25-2 hours
Sex incidence	female 75%	male 85%
Onset in childhood	25	<1
Unilateral pain	65	100
Recurrence in bouts	0	80
Associated features:		
nausea, vomiting	85	45
blurring of vision	common	8
lacrimation	uncommon	85
blocked nostril	uncommon	50
ptosis, miosis	uncommon	25
hyperalgesia of face, scalp	65	15
teichopsia, photopsia	40	<1
polyuria	30	7
Past health:		
vomiting in childhood	25	7
Family history:		
migraine	50	20
Biochemical changes:		
fall in plasma serotonin	80	0

There is even an experimental model of migraine. After the subcutaneous injection of rather large amounts (2.5 mg) of reserpine, a vascular headache appears in four to six hours in patients who have spontaneous migraine headaches.[11] The platelet serotonin also drops in response to reserpine. This response of serotonin to reserpine also occurs in nonmigrainous patients and they do not experience headache after the injection of reserpine. Furthermore, a reserpine-induced headache can be blocked with methysergide, but the decrease in platelet serotonin in unaffected. It is not at all clear what the decrease in serotonin has to do with the fundamental mechanism of headache; it may be an epiphenomenon. Of course, what happens in the central nervous system need not be reflected by changes in peripheral blood; serotonin-related metabolic events in neurons is perhaps more important than what is happening in platelets. Inasmuch as there is no animal model of migraine, this is impossible to test in our current state of knowledge.

There are other drugs which have been shown to be useful in the prophylaxis of migraine for which there is little or no evidence of serotonin antagonism or of vasoconstriction—propranolol,[12] clonidine,[13] tricyclics.[14] My own working hypothesis is that they depress central vasomotor instability; there are very few data that bear on this, however.

I want to turn now to another variant of migraine. It is useful to regard this disorder as migraine because it is responsive to the same group of pharmacological agents. In all other ways it is different. It has many names: migrainous neuralgia, cluster headache, red migraine, Horton's

histaminic cephalgia, Sluder's neuralgia and others.[15] The mechanism of this disorder probably involves intracranial arterial vasodilatation. It occurs predominantly in men, whereas migraine most often occurs in women (Table 4). It starts in the fourth and fifth decade, whereas migraine begins in childhood through the third decade. Cluster headaches characteristically waken people from sleep. They are associated with eye pain that is generally nonpulsatile in quality and are not usually associated with scintillating scotomata or vomiting. Often they are associated with tearing and reddening of the eye, puffiness of the periorbital tissue, stuffiness of the nose ipsilaterally and as the pain wears off in 10 to 20 minutes—these are short bursts of pain—the nose begins to run. All of these occur on the same side as the pain. The attacks occur one to several times per day for several weeks, stop for a while, and then recur. This cluster tempo is distinctive. There is no diminution of platelet serotonin in this condition; nor does there tend to be a high familial prevalence of the condition, as there does in migraine. These disorders are quite different genetically, clinically and biochemically. Yet the same group of drugs is effective for all of these patients.

What we have called migraine today is strictly an operational gesture. Your patients will benefit from your recognition of this common problem. In the not too distant future, several different disorders with distinctive mechanisms will probably emerge from this patient population. Until then, let us all keep our minds open regarding the nature of this disorder. We have certainly come a long way from the notion that migraine is primarily a psychosomatic disorder, a prevalent view 20 years ago.

REFERENCES

1. Hanington E, Harber AM: The role of tyramine in the aetiology of migraine, and related studies on the cerebral and extracerebral circulations. Headache 8:84-97, Oct 1968
2. Horwitz D, Lovenberg W, Engelman K, et al: Monoamine oxidase inhibitors, tyramine, and cheese. JAMA 188:1108-1110, Jun 29, 1964
3. Price K, Smith SE: Cheese reaction and tyramine. Lancet 1:130-131, Jan 16, 1971
4. Sandler M, Youdim MB, Hanington E: A phenylethylamine oxidising defect in migraine. Nature 250:335-337, Jul 1974
5. Fay T: Atypical facial neuralgia, a syndrome of vascular pain. Ann Otol Rhinol Laryngol 41:1030-1062, Mar 1932
6. Prusiner SB, Raskin NH: Carotodynia—A remediable vascular pain in the neck. Neurology 23:398, Apr 1973
7. Raskin NH, Knittle SC: Migraine: thermal and orthostatic phenomena. Neurology 25:379-380, Apr 1975
8. Dalessio D: On migraine headache: serotonin and serotonin antagonism. JAMA 181:318-321, Jul 28, 1962
9. Anthony M, Hinterberger H, Lance JW: Plasma serotonin in migraine and stress. Arch Neurol (Chicago) 16:544-552, May 1967
10. Lance JW: The Mechanism and Management of Headache. London, Butterworths, second edition, 1973, 205 pp
11. Tandon RN, Sur BK, Nath K: Effect of reserpine injections in migrainous and normal control subjects, with estimations of urinary 5-hydroxyindoleacetic acid. Neurology 19:1073-1079, Nov 1969
12. Wideroe TE, Vigander T: Propranolol in the treatment of migraine. Br Med J 2:699-701, Jun 1974
13. Shafer J, Tallett ER, Knowlson PA: Evaluation of clonidine in prophylaxis of migraine. Double-blind trial and follow-up. Lancet 1:403-407, Feb 19, 1972
14. Gomersall JD, Stuart A: Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. J Neurol Neurosurg Psychiatry 36:684-690, Aug 1973
15. Lance JW, Anthony M: Migrainous neuralgia or cluster headache? J Neurol Sci 13:401-414, Aug 1971

Presence of Abscess

In general, the problem of pus for the surgeon is the problem of diagnosing the cause of unexplained fever. After we have gone through the regular ritual of looking at the urine, looking at the lungs, looking at the wound and looking for phlebitis, one of the common causes of fever today, we are ready to consider abdominal abscess. I make it a cardinal point in my practice never to explore the abdomen or the chest looking for an abscess that I have not already found with a needle or by palpation, feeling a mass in the abdomen. I never explore for an abscess. I have got to find it. And the way to find it is by repeated, careful, deliberate, systematic physical examination by the same observer several times a day, every day. It is the fever that is the tipoff to the presence of the abscess. The leukocyte count helps me not at all.

—MARK M. RAVITCH, MD, *Pittsburgh*

Extracted form *Audio-Digest Surgery*, Vol. 22, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057