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DRUG THERAPY

JAN KOCH-WESER, M.D., *Editor*

Nonsteroidal Antiinflammatory Drugs

(Second of Two Parts)

LEE S. SIMON, M.D., AND JOHN A. MILLS, M.D.

NEW NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Within the past 10 years, a number of new NSAID's have become available in the United States. Most are representatives of two groups of compounds, the indoles, of which the prototype is indomethacin, and the phenylpropionates. Other chemical classes that have antiinflammatory properties but have not been widely exploited clinically include the pyrazolones, represented by phenylbutazone and its metabolite oxyphenylbutazone, the quinazolones, imidazoles, and phenothiazines. Several anthranilic acid derivatives, the fenamates, have been available in Europe for almost a decade but have not achieved an important status. The inhibition of prostaglandin biosynthesis appears to be a major mechanism of the antiinflammatory effects of all these drugs.⁵⁹

Sulindac

Sulindac (Fig. 3) has recently been released in the United States after some years of use in Europe. It bears a chemical resemblance to indomethacin but is a substituted indene rather than an indole, and it has a sulfinyl group on the phenyl substituent that appears to be responsible for some of its properties.¹⁰²

This drug was synthesized as the result of a search for a compound as effective as indomethacin but with less ulcerogenic potential. Its reduced tendency to produce ulcers may be due to the fact that the active drug is not present as such in the stomach.¹⁰³ Sulindac, given as the sulfoxide, is rapidly absorbed from the stomach and upper intestinal tract and is converted by the liver cytochrome system to several metabolites that reflect different degrees of oxidation of the methyl sulfinyl constituent. The conversion of sulfoxide to sulfide is reversible, whereas the reaction to sulfone is not. The sulfide derivative has a relatively prolonged triphasic plasma disappearance with a half time of 16 hours for the slowest phase. It is eliminated from the plasma, predominantly by excretion in the bile, but it is subject to enterohepatic circulation. In the enterohepatic circulation it is mostly in the form of sulindac, the sulfoxide parent compound, and provides a pool of drug available for conversion to the sulfide.¹⁰⁴ The sulfide appears to be the important antiinflammatory metabolite and is the only one that inhibits prostaglandin biosynthesis.¹⁰⁵ Peak plasma

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levels of 0.1 to 0.2 mg per 100 ml occur two to three hours after an oral dose of 200 mg. Steady-state plasma levels of the sulfide are about 0.4 mg per 100 ml and are reached after four to five days of therapy with 200 mg twice daily by mouth.

Sulindac is available in the United States in tablets of 150 and 200 mg. Because it is metabolized slowly it can be given effectively in a twice-daily dosage. Studies in Europe have shown it to be as effective in rheumatoid arthritis and osteoarthritis as indomethacin or aspirin.⁵⁹ It is also useful in the treatment of articular gout.¹⁰⁶ In one study it was more effective than ibuprofen in osteoarthritis of the hip (the dose of ibuprofen, however, was only 1200 mg per day).¹⁰⁷ Sulindac has been found less satisfactory than indomethacin and phenylbutazone for ankylosing spondylitis.⁵⁹ A recent review details sulindac's efficacy in various inflammatory diseases.¹⁰⁸

Gastrointestinal irritation and dyspepsia, as well as occult blood loss, are less severe during treatment with sulindac than with aspirin and only slightly greater than during placebo administration.¹⁰⁸ Huskisson reports that only 25 per cent of the patients have gastrointestinal problems; constipation is the predominant one. Sulindac seems to have less effect on the central nervous system than indomethacin, possibly because it has an indene rather than the indole nucleus present in both indomethacin and serotonin, an important mediator in the central nervous system. Like indomethacin, sulindac inhibits collagen-induced platelet aggregation in vitro.¹⁰⁹

Sulindac is thus another NSAID that may be better tolerated than aspirin or indomethacin. It has much the same therapeutic spectrum as indomethacin, but whether it is as effective clinically remains to be determined. Like the other NSAID's, sulindac appears to produce wide variations in individual responsiveness.

Ibuprofen

Ibuprofen (Fig. 4) was the first phenylpropionate to be marketed in the United States. The phenylpropionates are a class of compounds with analgesic, antipyretic, and antiinflammatory activity in animals. All appear to inhibit prostaglandin synthesis, some more effectively than others.⁵⁹ Ibuprofen is well absorbed, and peak plasma levels of 15 to 20 μ g per milliliter are achieved about one to two hours after a single dose. The half-life is about 3.5 hours. The drug is mostly metabolized in the liver, with less than 10 per cent excreted unchanged in the urine and bile.¹¹⁰

Ibuprofen was found to be a weak antiinflammatory drug at the doses initially recommended, although its efficacy as an analgesic was established. Boardman et al.¹¹¹ found that neither 600 nor 900 mg of ibuprofen was better than a placebo in a study of 20 patients with rheumatoid arthritis and 19 patients with osteoarthritis. Godfrey and de la Cruz¹¹² showed that ibuprofen at a dose of 2400 mg per day had considerably greater antiinflammatory effects than it did

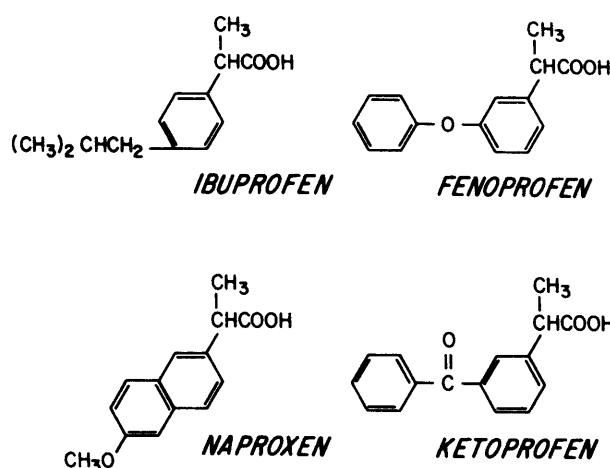


Figure 4. The Propionic Acid Derivatives.

at 1200 mg per day and that at 1200 mg per day its actions are predominantly analgesic. However, when technetium uptake was used as a measure of inflammation, that difference did not emerge until the fourth week. There was no difference in the incidence of side effects between patients on the high and low doses. Ibuprofen is useful in osteoarthritis of the hip, in rheumatoid arthritis, and, at its highest recommended dose, in gout.^{88,113} It may not be as effective as other propionic acid derivatives or salicylate in rheumatoid arthritis.¹¹³⁻¹¹⁵ Recently, ibuprofen has been shown to be more effective than a placebo in the treatment of dysmenorrhea.¹¹⁶

Ibuprofen is well tolerated.¹¹⁵ The recommended dosage is 1200 to 2400 mg per day. It is available in tablets of 300, 400, and 600 mg. Gastrointestinal effects include nausea and dyspepsia, but bleeding occurs rarely. In addition, like aspirin, ibuprofen may exacerbate bronchospasm through the inhibition of prostaglandin biosynthesis.³⁹ Reversible toxic amblyopia has been reported.¹¹⁷ Ibuprofen can inhibit platelet aggregation,¹¹⁰ and it has been shown to cause reversible rises in blood urea nitrogen and serum creatinine.⁴⁴ As with other NSAID's, both effects appear to be due to interference with prostaglandin biosynthesis. Ibuprofen has been reported not to interfere with the protein binding of warfarin-like drugs.¹¹⁸ There are two reports of the occurrence of a meningeal syndrome in patients with systemic lupus erythematosus who had been receiving ibuprofen.¹¹⁹

Fenopropfen

Fenopropfen (Fig. 4), as either the sodium or calcium salt, is a phenoxyphenyl propionic acid. The calcium derivative is more commonly used. It is well absorbed, achieving a peak plasma level of 20 to 30 μ g per milliliter two hours after a single oral dose, with a plasma half-life of two to three hours.¹²⁰ Most of the drug is excreted as the glucuronide in the urine. Absorption may be impaired when the drug is taken with aspirin, food, or phenobarbital, although this impair-

ment may not be clinically important. The drug is available in 300-mg capsules, and the recommended dosage is 2.4 g per day. Steady-state plasma levels are reached within the first 24 hours of therapy. Although studies have shown that fenoprofen is as effective as aspirin,¹²¹ Fries et al. could demonstrate no advantage of fenoprofen over high-dose aspirin in the treatment of rheumatoid arthritis.¹²² There was more gastrointestinal toxicity with aspirin. In a study of patients with rheumatoid arthritis, Huskisson et al. found that fenoprofen and naproxen were favored by more subjects than ibuprofen or ketoprofen, another propionic acid derivative.¹¹³ Fenoprofen is also effective treatment for acute gouty arthritis.¹²³ Brooke compared aspirin and fenoprofen in the treatment of osteoarthritis and later evaluated varying doses of fenoprofen in osteoarthritis.¹²⁴ Patients seemed to prefer fenoprofen to aspirin, but there was no substantial difference between the two drugs. Both were better than a placebo. Some patients were later shown to obtain relief with relatively small doses of fenoprofen. Fenoprofen, 600 mg every six hours, was subjectively more effective than 975 mg of aspirin every six hours.

Fenoprofen is relatively well tolerated as compared with aspirin and causes less occult gastrointestinal bleeding.¹²⁵ Chernish et al. also found on endoscopy that there was less gastric irritation from a daily dose of 2400 mg of fenoprofen than from 3900 mg of aspirin.¹²⁶ Nevertheless, dyspepsia remains the most common side effect and seems to be more common with fenoprofen than with ibuprofen. Hypersensitivity rashes of various types have been described.

Naproxen

Naproxen (Fig. 4) is another propionic acid derivative with a relatively long half-life. It is well absorbed in the upper gastrointestinal tract and is highly bound to plasma albumin.¹²⁷ Because of its half-life of 13 hours, it is suitable for twice-daily administration. It takes approximately three days for equilibrium to be reached. It is excreted almost entirely in urine, mainly as an inactive glucuronide metabolite.¹²⁷ Because of the rapid urinary excretion of the free drug, plasma levels are limited by the extent of plasma protein binding and increase little at doses greater than 500 mg twice daily.¹²⁸ This fact may limit naproxen's toxicity. The occurrence of peak blood levels is delayed when naproxen is administered with a full meal or when magnesium oxide or aluminum hydroxide buffering compounds are given, but sodium bicarbonate increases its absorption. These effects do not appear clinically important.

Naproxen is available as 250-mg tablets. It has been shown to be more effective than a placebo^{129,130} and as effective as indomethacin in rheumatoid arthritis.¹³¹ In addition, in several studies in which a 500-mg dose of naproxen was compared with aspirin in usual doses in rheumatoid arthritis, naproxen was better tolerated.¹³² In another study, naproxen was again as effective as aspirin, but there was no difference in side ef-

fects.¹³³ Myhal et al. reported that naproxen was well tolerated for over two years in 27 patients with rheumatoid arthritis.¹³⁴ Mäkelä¹³⁵ used naproxen or aspirin to treat two groups of children, aged three to 16 years, who had rheumatoid arthritis. When 10 mg of naproxen per kilogram was taken daily, it was found to be as effective as aspirin, 60 to 80 mg per kilogram per day, yet with fewer side effects. No liver abnormalities were seen. A prolonged bleeding time was observed in 42 per cent of the children treated with naproxen.

Naproxen has also been shown to be as effective as aspirin in the treatment of osteoarthritis of the hip and knee.¹³⁶ Sturge et al.¹³⁷ found that naproxen, 750 mg as a single dose followed by 250 mg twice daily until inflammation had subsided, is comparable to phenylbutazone in alleviating acute gout. It is as effective as indomethacin in the treatment of sports injuries.¹³⁸ It also has been found to relieve dysmenorrhea.¹³⁹ The mechanism of this effect on dysmenorrhea is not known, although inhibition of prostaglandin synthesis is thought to be important.

As noted previously, there has been much debate about whether the simultaneous administration of aspirin and other NSAID's causes decreased efficacy of either or both drugs.¹⁴⁰ Segre¹²⁷ showed that concomitant administration of aspirin and naproxen decreased naproxen blood levels in man (levels decreased by 16 per cent), which he thought was not clinically important. The postulated mechanism is displacement of naproxen by aspirin from plasma protein-binding sites, thus facilitating naproxen's metabolism and excretion. However, Wilkens and Segre¹⁴⁰ later reported that 250 mg of naproxen twice daily along with aspirin was subjectively more effective than aspirin therapy alone. There was no increase in side effects with the two-drug regimen.

Overall, naproxen causes less gastrointestinal irritation than aspirin.¹⁴¹ However, there have been several reports of naproxen-induced gastrointestinal hemorrhage.^{142,143} Lehtola et al.,¹⁴⁴ in an endoscopy study, found changes in the gastric mucosa in four of six healthy subjects given naproxen. The observed lesions did not correlate well with symptoms. Roth and Boost¹⁴⁵ evaluated 58 patients with superficial esophageal, gastric, and duodenal lesions who were given naproxen for therapy of rheumatoid arthritis. They concluded that naproxen can be safely administered to patients with histories of peptic ulcer or hiatus hernia, although the patients should be closely followed. Other side effects of naproxen include stomatitis, headache, vertigo, lightheadedness, dyspepsia, nausea, and rash.⁵⁹ Naproxen increases bleeding time by inhibiting platelet aggregation.

When given during pregnancy, naproxen crosses the placental barrier 20 to 30 minutes after oral administration. Because of its presence in the fetus, the drug may potentiate neonatal jaundice through competitive binding to serum albumin, thereby elevating free bilirubin.¹⁴⁶

Naproxen appears to be well tolerated, effective in many different conditions, and, because of its long half-life, it may be given in twice-daily form, which has been found to improve therapeutic compliance.

Tolmetin

Tolmetin (Fig. 3) is a pyrrole derivative that has a structural resemblance to indomethacin but an action and toxicity more like those of the propionic acid derivatives.⁵⁹ It is well absorbed and highly protein bound. It has a half-life of 60 minutes and is excreted in the urine partly unchanged, partly conjugated, and as an inactive dicarboxylic acid metabolite.¹⁴⁷ When given concomitantly with aspirin, it is displaced in competitive fashion from its protein-binding sites, with the result that its metabolism is accelerated.

The drug is available in tablets of 100 and 200 mg. Some authors have concluded that in the treatment of rheumatoid arthritis, tolmetin is more effective than a placebo,¹⁴⁸ better than aspirin according to subjective evaluation, and equal to indomethacin in terms of effectiveness and better in terms of tolerability.¹⁴⁹ Contrary to the experience with naproxen, combined therapy with tolmetin and aspirin was no better than aspirin alone.¹⁵⁰ Of the patients who did not tolerate gastrointestinal or central-nervous-system effects of indomethacin, 75 per cent could tolerate tolmetin.

Objective and subjective side effects of tolmetin are similar to those of other NSAID's. In one study, occult fecal blood loss was statistically greater with tolmetin than during control periods but was less than during therapy with aspirin or indomethacin.¹⁵¹ Ehrlich and Roth¹⁵² found that gastrointestinal side effects were the main problem in 30 per cent of 420 patients with rheumatoid arthritis who were treated with tolmetin. These symptoms included nausea, vomiting, diarrhea, dyspepsia, anorexia, abdominal pain, and stomatitis. In the same group of patients, 3.6 per cent had peptic ulcers during 27 months of treatment with tolmetin. Other side effects included headache, dizziness, and hypersensitivity reactions such as macular rash or urticaria. Tolmetin causes edema due to sodium retention in about 2 per cent of patients. Abnormal results of liver-function tests and a reversible rise in blood urea nitrogen have been reported.¹⁵² Transient leukopenia and a case of agranulocytosis have been ascribed to tolmetin.¹⁵³

Tolmetin, like other NSAID's, inhibits prostaglandin synthesis, and this inhibition is postulated as the mechanism for its antiinflammatory effects. Tolmetin prolongs template bleeding time, but the effect is reversible; there is a return to pre-drug level by the third day after cessation of therapy.¹⁵⁴

Mefenamic Acid

The fenamates are anthranilic acid derivatives that are well absorbed after an oral dose, reaching peak plasma levels two hours later. Their half-life is four to six hours. Mefenamic acid (Fig. 5) is the only one

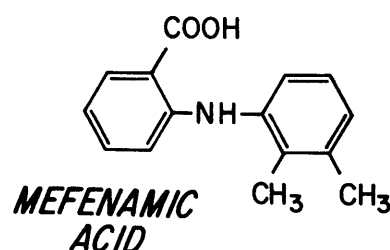


Figure 5. A Representative of the Fenamates.

available in the United States, although flufenamic acid and tolfenamic acid are available elsewhere. They inhibit prostaglandin synthesis and, in addition, seem to reduce the activity of prostaglandins, possibly by blocking prostaglandin receptors on cells.¹⁵⁵ The major gastrointestinal side effect was diarrhea in 12 per cent of patients treated with mefenamic acid.⁵⁹ Its use for more than one week is not recommended because of the possibility of more serious gastrointestinal effects or nephrotoxicity. Other side effects include gastrointestinal bleeding, rashes, hemolytic anemia, and bone-marrow hypoplasia. It may potentiate warfarin anticoagulants and, like aspirin, may exacerbate asthma in some patients. Mefenamic acid as an analgesic is equivalent to aspirin, but it is not more effective in the treatment of rheumatoid arthritis.¹⁵⁶

Thus, mefenamic acid does not appear to be better than aspirin and has certain unique side effects. Like other NSAID's, it is useful for treatment of dysmenorrhea.¹⁵⁷

OTHER NONSTEROIDAL ANTIINFLAMMATORY DRUGS

There are a number of NSAID's not available in the United States that have been used elsewhere for several years. These include both propionic acid derivatives and anthranilic acid derivatives. All have been shown to inhibit prostaglandin synthesis to varying degrees and to be antiinflammatory and analgesic.

Tolfenamic acid is an anthranilic acid derivative available in Europe since the early 1970's. Like the fenamates, it may be as effective as aspirin in treating rheumatoid arthritis¹⁵⁸ and osteoarthritis of the knee.¹⁵⁹ Gastrointestinal irritation is the most common side effect.¹⁶⁰

Several other propionic acid derivatives in use in Europe may become available in the United States. Ketoprofen (Fig. 4) has been shown to be more effective than a placebo but inferior to indomethacin in the treatment of rheumatoid arthritis.^{161,162} Montrone et al. concluded that 200 mg per day of ketoprofen is preferred to 1200 mg of ibuprofen in rheumatoid arthritis.¹⁶³ It may be as effective as indomethacin in the treatment of osteoarthritis of the hip. Huskisson¹¹³ found that ketoprofen, although equivalent to ibuprofen as therapy for rheumatoid arthritis, had more side effects. Ketoprofen is given as 50-mg tablets three or four times daily. Gastric side effects are the most com-

mon problem but may be less frequent than with naproxen or indomethacin.^{164,165} It also has been reported to cause pseudotumor cerebri when used to treat Bartter's syndrome.¹⁶⁶

Benoxaprofen, indoprofen, fenbufen, and pirofen are also propionic acid derivatives. Benoxaprofen may be given in once or twice-a-day dosages. It is a weak inhibitor of prostaglandin synthesis.¹⁶⁷ In studies with rats it has been shown to interfere with migration of leukocytes into inflammatory tissue *in vivo*. Indoprofen has been reviewed by Huskisson and Scott.¹⁶⁸ It appears to be highly protein bound and is excreted mainly as a glucuronide in the urine. Its half-life is 3.5 hours; it appears to be best given four times per day. A similar schedule is recommended for fenbufen. All three drugs are claimed to be better than a placebo, equal to aspirin, and better than 1200 mg per day of ibuprofen in the treatment of rheumatoid arthritis.¹⁶⁹ Pirofen has a half-life of seven hours, is excreted by the kidneys, and is claimed to be equal to aspirin in the treatment of rheumatoid arthritis.^{170,171}

Fendosal is an arylindole chemically related to indomethacin but less potent as an antipyretic. It appears to have similar toxicity.¹⁷² Proquazone, a quinazolinone derivative, has been compared favorably with indomethacin and naproxen in patients with rheumatoid arthritis.¹⁷³ Diclofenac is a phenylacetic acid similar to aclofenac but without the latter's high incidence of dermatitis. It has been proved better than a placebo and equal to indomethacin and aspirin in the treatment of rheumatoid arthritis, and it has similar side effects.¹⁷⁴

CONCLUSION

The nonsteroidal antiinflammatory agents have been studied intensively in recent years. Much of this effort has been devoted to discovering how the NSAID's affect the complex process of inflammation. After Vane et al. discovered that aspirin and indomethacin were potent inhibitors of prostaglandin biosynthesis, such inhibition was found to be a property of all the NSAID's in current use. Prostaglandins both directly and through their influence on cyclic nucleotide levels in cells and tissues are important modulators of the inflammatory response and its consequences. Whether interference with cyclooxygenase function is the principle manner by which the NSAID's reduce inflammation remains unknown. It is evident that the largest tolerated doses of these agents do not completely arrest the inflammatory response or its consequences; however, the symptoms of inflammation are reduced to a greater extent than is possible with strictly analgesic drugs.

The use of NSAID's carries some risk. Their effects on the stomach and on platelet physiology are well defined. These side effects are a direct consequence of mechanisms that are also responsible for the therapeutic actions, and precautions must be taken to reduce them. However, until nontoxic drugs that arrest the inflammatory process are available, the drugs

reviewed in this article will remain therapeutically important.

A baffling but apparently important aspect of the use of the NSAID's is the marked variability in clinical response to a given drug between patients who appear to have the same condition and whose serum levels of the drug are similar. Whether this phenomenon is caused by individual variations in drug handling or as yet unrecognized differences in the inflammatory response is not known. Thus, physicians prescribing these agents should try several of them sequentially when the response to one is inadequate. Since maximum symptomatic benefit is usually obtained within seven days, such trials are relatively acceptable to the patient. It should be remembered also that variable compliance by patients may complicate management.

Patients with chronic diseases such as rheumatoid arthritis or osteoarthritis are often treated with multiple-drug regimens when a single agent proves inadequate. Highly plasma-bound drugs compete with each other for binding sites. Certain effects may be enhanced as more drug is freed, but if it is then rapidly cleared by the kidney, the result may be counterproductive. A recent review includes an evaluation and summary of the interactions among nonsteroidal antiinflammatory agents.¹⁷⁵

The newer NSAID's are considerably more expensive than most salicylate preparations. The monthly cost to the patient for full antiinflammatory doses of a number of NSAID's is compared in Table 1. The range shown was obtained from the *Drug Topics* "Red Book," a trade publication, and from a survey of a number of pharmacies in the Boston area in mid-1979. Since the therapeutic difference is frequently marginal, cost may be a relevant consideration.

In conclusion, the newer NSAID's are not more effective in general than aspirin in the treatment of rheumatoid arthritis, although adverse symptoms occur less often with these drugs than with aspirin.

Table 1. Cost Comparison of Nonsteroidal Antiinflammatory Drugs.

DRUG	HOW SUPPLIED	AVERAGE DAILY DOSE	AVERAGE COST TO PATIENT PER MONTH (\$)
Aspirin	300-mg tablets	3.6 g	3.56-5.75
Buffered aspirin	300-mg tablets	3.6 g	5.00-12.00
Ascriptin	325-mg aspirin & 150 mg Maalox	3.6 g	7.80-10.20
Choline magnesium trisilicate	500-mg tablets	4 g	25.00
Enteric coated aspirin	300-mg tablets	3.6 g	6.10-6.90
Fenoprofen	300 & 600-mg capsules	1.8 g	23.20-29.00
Ibuprofen	300, 600, & 400-mg tablets	2.4 g	22.00
Indomethacin	25 & 50-mg capsules	100 mg	18.60-22.00
Naproxen	250-mg tablets	0.5 mg	14.00-29.70
Phenylbutazone	100-mg capsules	300 mg	14.00-19.50
Sulindac	150 & 200-mg tablets	300 mg	7.80-11.90
Tolmetin	200-mg tablets	1.2 g	18.60-23.40
			22.80-30.00

On the other hand, in the case of acute inflammatory disorders other than rheumatoid arthritis, and in the seronegative spondyloarthropathies, the newer NSAID's are frequently more effective than aspirin. In addition, the newer NSAID's allow a smaller number of pills to be taken, thereby possibly improving the patient's compliance with the therapeutic regimen.

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BY THE LONDON POST

JOHN LISTER, M.D.

More Heart Transplants — Dial-a-Doctor — Parliamentary Report — Dr. Franz Ingelfinger

TWO cardiac surgical units in Britain have embarked on new programs for cardiac transplantation: one is at Papworth Hospital, East Anglia, where the surgeon in charge is Mr. Terence English, and the other is at Harefield Hospital, Middlesex, where the surgeon is Mr. Magdy Yacoub.

So far 11 transplantations have been carried out in this series. The one immediate postoperative death occurred at Harefield in the only female patient in the

series, and one of the male patients at Harefield died after the development of signs of rejection.

There has been much public interest in this resumption of cardiac transplantation, with renewed debate about the ethics and cost effectiveness of the procedure in relation to other priorities. There is also concern about ensuring that heart transplantations are only carried out in centers that are fully equipped for such procedures, and the Department of Health and Social Security (DHSS), which has given qualified approval to the new programs, has issued firm guidance on this point. In a letter¹ to all senior medical administrators, the chief medical officer has emphasized the need for any unit carrying out cardiac transplantations to meet the criteria recommended by the advisory panel on organ transplantation. Such units should already be centers for advanced cardiac surgery, should have donor hearts of high quality available, should have sufficient medical, nursing, and technical staff to maintain the program, and should have adequate support services in pathology, immunology, and microbiology available at all times.

In addition, centers performing cardiac transplantation should have carried out experimental work on immunology, circulatory support, and organ-preservation systems. Finally, it is emphasized that heart transplantations should only be carried out as part of a planned program.

Advances in many fields in medicine have occurred as a result of the efforts of hard-working, persistent enthusiasts, who have been relentless in their pursuit of their aims even though they have been handicapped by lack of funds and often by less than ideal working conditions. Mr. English and Mr. Yacoub are both outstanding examples of such enthusiasts, and the recognition of their enthusiasm and their acknowledged competence has brought financial support for their programs.

The DHSS estimates that the revenue cost for each patient submitted to cardiac transplantation is £17,300, and the government is making a special allocation of up to £100,000 to improve the operating rooms and intensive-care facilities at Papworth. On the other hand, it has been made clear that the DHSS cannot accept an unqualified ongoing commitment for these programs until the wider implications for the National Health Service (NHS) have been studied.

Meanwhile, however, the Papworth² unit and the Harefield³ unit have each received £300,000 from private benefactors, so that the immediate financial requirements of each unit are assured. From the long-term viewpoint, the *Lancet* admits that the case for putting resources into preventive rather than curative cardiology medicine is strong, since the control of smoking, obesity, and hypertension would save many more lives than cardiac transplantation could ever hope to save. But the benefits of preventive medicine are slow to become manifest, and it is the present