# *TRIAZURE AND PUBLIC DRUG POLICIES**

*SEYMOUR SHUBIN*†

> *Triazure is a classic example of a highly effective drug which is useful to a small number of patients with a serious disease but which also carries a serious risk of harm in a fraction of those who take it. Benefit/risk decisions on such drugs are always difficult, controversial. Many of us at the Food and Drug Administration have lived through several soul-searching decisions on this drug, and I am happy to share our thinking on these complex decisions with your Subcommittee. I know of no better example than Triazure to illustrate that benefit/risk decisions on drugs require not only a keen analysis of the scientific data but also the thoughtful judgment of specialists experienced in the care of sick patients.* [J. RICHARD CROUT, M.D., Director Bureau of Drugs, FDA, in a statement before the House of Representatives' Subcommittee on Intergovernmental Relations and Human Resources, October 27, 1976]

The subcommittee hearing lasted just 1 day. The vast majority of the general public—indeed, of the medical community—probably never even knew it had been held. Yet even if they knew what had prompted it and what the outcome was, the overwhelming odds are that they would never suspect that anything had occurred that could possibly affect their clinical practice. After all, the hearing dealt with a drug for a type of psoriasis that affects only a relatively few people. Moreover, the Food and Drug Administration had already ordered the drug withdrawn because of its dangerous side effects, and the purpose of the hearing was to investigate why the FDA had ever permitted the drug to be placed on the market in the first place. And in any event, a new type of therapy was on the horizon that some asserted might prove even more effective than the drug that had been withdrawn.

Still, none of this diminishes the importance of the hearing and the events leading up to it. Instead, deeply disturbing questions spring up. Will political pressures, for instance, negate a medical decision that the benefits of a drug are so much greater than its risks that it should be marketed? Is Congress forcing the FDA in a direction where it will not

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†122 Harrogate Road, Overbrook Hills, Pennsylvania 19151.

permit a drug to be made available if it has serious toxicity? Are physicians not to be trusted to give a drug for the disease for which it is intended? Are they not to be trusted to use their judgment about alerting patients to possible side effects? Cannot the victims of maddening, horrible diseases be given the choice of whether or not to risk a serious, perhaps even fatal, adverse drug reaction for the far greater chance of dramatic help? How can a small pharmaceutical firm, with a potential miracle drug, carry out years of expensive, possibly bankrupting, testing? What can be done if such a firm is forced for financial reasons to drop the product? Will the FDA be able to enlist high-caliber consultants if valid decisions continue to be shredded by government committees? Was the hearing, in fact, politically motivated? If not, why were most of the witnesses people who were *against* having the drug marketed? Why did the subcommittee not summon more of the physicians who voted *for* making it available? And why were other physicians who support the drug not permitted to testify, even though they requested such opportunity?

"The heartbreak of psoriasis," states the well-known advertisement. In some instances, that is a serious understatement. Psoriasis is, of course, a skin disease—a chronic, inflammatory, scaly, sometimes itchy disease of unknown etiology. Its victims may have just a few skin plaques, may be affected in individual sections of their body, or may be covered almost totally with lesions (even their scalp, nails, lips, and eyes). It is estimated that 2 million to 8 million people in the United States suffer from the disease.

Patients with milder psoriasis are generally treated with skin creams and ointments, particularly tar-based or corticosteriod preparations, and by ultraviolet light. But a small group of unfortunate patients responds poorly to topical medications. Dr. Wilma F. Bergfeld, assistant professor of dermatology at the Cleveland Clinic and a member of the Dermatology Advisory Committee to the FDA who had voted to market the new drug, showed a series of slides at the subcommittee hearing. Here are some of her comments:

> Here is a middle-aged woman and you see the involvement of her buttock and her upper extremities. This is very itchy. These patients pick at it. They do not wear clothing that reveals this kind of skin change, a very embarrassing condition. . . . This young man is 18 years old and he is generally red all over. His skin is very itchy and extremely painful. This young man tried to commit suicide two times in the last three years because of this skin disorder. . . . Another example of severe psoriasis of the palms. . . . [Notice] the nail involvement here—people with this disorder do not show their hands. They do not have businesses or work with people where their hands have to show. . . . The nails can be painful, can have secondary bacterial infections. . . . Here are some nail changes and the arthritis that occasionally goes along with psoriasis. We see psoriatic arthritis in approxi-

mately 10 percent of the cases of psoriasis vulgaris. We see . . . shortening of the fingers and some distortion.

During the past 5 years, she told the subcommittee, one other psoriatic patient at the Cleveland Clinic had attempted suicide twice. And there is a high incidence of alcoholism among the large number of psoriatics they see.

Not that there has been no treatment for severe psoriasis. In the 1960s, a systemic drug, methotrexate, which is used in cancer therapy, had been found to be effective in treating refractory psoriasis. However, the drug—an antimetabolite—can trigger liver damage, bone-marrow depression, and death. Consequently, many patients cannot take it.

It was against this background, said Bureau of Drugs Director J. Richard Crout in his prepared statement at the hearing, that the FDA first became interested in another potential treatment for severe psoriasis—another systemic drug, azaribine.

In the mid-1960s, Dr. Paul Calabresi, now in the Department of Medicine at Brown University School of Medicine, discovered that azaribine was effective in treating refractory psoriasis. A small drug firm, Calbiochem, located in LaJolla, California, took over the development of the drug under the trade name of Triazure.

On December 12, 1969, Calbiochem submitted a new drug application (NDA) to the FDA to market Triazure for severe psoriasis and/or psoriatic arthritis. The FDA required further preclinical data, including carcinogenicity studies, which resulted in a number of withdrawals and resubmissions of the application. Then in December, 1971—2 years after the original submission—the FDA issued a letter of nonapproval based on the fact that only 132 patients had been treated, which was felt to be insufficient to establish the drug's safety, and stated that further study was needed to establish the possible effectiveness of lower dosages of the drug. But "an important and encouraging finding in these early studies," Dr. Crout told the subcommittee, "was the lack of liver toxicity. Thus, Triazure showed from the start a promise of usefulness in patients with liver damage who could not take methotrexate."

Calbiochem resubmitted the application in June 1972; clinical studies had now been conducted on a total of 377 patients. These new studies, however, revealed that 14 patients had experienced thrombotic episodes, a phenomenon that had not shown up before.

As a result of this finding, Crout continued,

The data on thromboembolic events were reviewed by Dr. Charles Anello, Division of Statistics, Bureau of Drugs, and by a consultant, Dr. Paul O. Stolley, then Associate Professor, Department of Epidemiology, the Johns Hopkins University School of Hygiene and Public Health. They were also reviewed by me. Our

reviews were all in basic agreement that approximately 2.5 to 4 percent of the 377 patients who had taken the drug up to that time had suffered a thromboembolic episode. These episodes consisted mainly of thrombophlebitis and myocardial infarction; in addition there was one case each of pulmonary embolism and aortic thrombosis and two cases of mesenteric vein thrombosis. Among these cases there were three deaths and three episodes requiring lifesaving surgery. Drs. Anello and Stolley and I also agreed that at least some of these events were probably drug-related since the four cases occurring in the 134 patients in controlled cross-over trials all developed during or after treatment with Triazure.

The pharmaceutical firm, however, argued that these occurred mainly in patients with "predisposing factors" to thromboembolism, "a thesis we found unconvincing."

Although the risk of thromboembolic complications seemed high, the medical review team looked on the drug as such an important advance, stated Crout, that

even this high risk did not appear necessarily unacceptable in view of the drug's efficacy and the condition for which it was intended. After several conferences with the Medical Officer and Division Director, I included in my review some recommendations intended to bring the benefit/risk question into sharper focus for subsequent discussions. Specifically, I recommended (*a*) that the staff draft proposed labeling appropriate for the drug including a box warning, (*b*) that the indication be limited to severe, recalcitrant psoriasis, (*c*) that the possibility be explored of a phase 4 study aimed at defining better the incidence of thromboembolic episodes and the possible relationship of predisposing factors to thromboembolism, and (*d*) that the Dermatology Advisory Committee review the data and labeling and concur in any decision for marketing.

Usually, there are three investigative phases that a new drug has to go through successfully before it can possibly be approved by the FDA. But in certain cases, as Crout wished explored here, a drug may go through a fourth phase. If the drug is considered important enough to be made available without too much further delay, but more information is wanted, the FDA may permit it to be marketed on condition that the pharmaceutical company conduct or support further studies on it.

On June 11, 1973, the FDA medical review team met with the Dermatology Advisory Committee—which is made up of non-FDA physicians—and the committee's consultants. The committee, agreeing that thromboembolism was the major safety problem, voted that the pharmaceutical firm conduct further studies before the drug was approved. The vote, however, was not unanimous against approval, nor did a single member suggest that the drug be turned down permanently because it was unsafe. The FDA issued a nonapproval letter to Calbiochem on June 26, 1973.

The FDA staff met with representatives from Calbiochem during the next several months to assist them in designing a protocol for a well-

controlled phase III study, but, Crout told the subcommittee, "Regrettably from our point of view, the firm devoted its attention not to this proposed protocol but to a new thesis first introduced by the firm at the Dermatology Advisory Committee meeting on June 11, 1973—namely, that Triazure is not associated with an increased risk of thromboembolic disease, but psoriasis itself is. This contention was based on three retrospective studies conducted at the University of California at San Francisco, Roger Williams General Hospital, and Wadsworth Veterans Administration Hospital. In our opinion the studies were inadequate and failed to demonstrate the point. . . .Nevertheless, it has been the firm's steadfast position since that time that Triazure has not been shown to carry a drug-related risk of thromboembolic episodes and that this apparently high incidence is due to the fact that psoriasis itself is a prominent risk factor."

Crout went on to state that, because of the concern over the thromboembolic problem, "and in order to advise on a protocol for the phase III study, we requested the firm, on July 30, 1973, to engage in a careful review of all cases of thromboembolism occurring up to that time in patients treated with Triazure. The review was to include complete medical histories, past and present, pre-treatment complications, and follow-up data where available. Calbiochem submitted this information on September 18, 1973. To our surprise, this submission was accompanied by a letter from Calbiochem stating that, in its view, the deficiencies outlined in our nonapproval letter issued only three months previously were now corrected."

This reopened the file, necessitating a new review as a pending new drug application. This submission contained information on 179 new patients, bringing the number to 556. Paul Stolley, the consultant epidemiologist, reviewed the data and found that 23 thromboembolic episodes were recorded, "an incidence of 4 per 100 treated patients." Said Crout, "The types of thromboembolic episodes reported were similar to those described previously. The patients who developed thrombosis did so within the first three to five weeks of therapy, while patients maintained on the drug for longer periods of time did not seem to have a progressively increasing risk. There were two deaths due to myocardial infarction among the 23 patients, for a case fatality rate of 9 per 100 thromboembolic episodes or an overall mortality of approximately 4 per 1,000 users of the drug."

Stolley's conclusion was that he could not prove by the figures themselves that the episodes were related to the drug and that the only way to demonstrate it was to conduct a placebo-controlled study in about 500 psoriatric patients. He did feel, however, that the episodes were probably drug related and that it would not serve any useful purpose to exclude patients from the study who did have "predisposing factors."

Although the company's new submission had led to some "refinement of the numbers" of thromboembolic episodes, Crout explained to the subcommittee, it had not led to a "basic change in our estimate of the degree of thromboembolic risk. In short, it was now becoming increasingly clear that further data were unlikely to reveal a markedly different picture in regard to this risk and therefore were unlikely to be of critical importance to the hard decision before the agency. The issue was whether, given this degree of risk and a prominent warning describing it in the labeling, the drug should still be approved on the grounds that it should be available to a limited population of seriously ill patients whose only alternative for systemic therapy was methotrexate."

On January 4, 1974, at Calbiochem's request, members of the drug firm and its consultants met with the FDA staff in an attempt to resolve the issues.

Crout stated that

> at that time we were also told that the firm wanted a final decision on the drug on the basis of the data at hand. Dr. William Drell, President of Calbiochem, indicated that the firm did not have the resources to consider an extended trial of the type recommended by Dr. Stolley prior to marketing approval but that the firm could support a careful study in the postmarketing period aimed at clarifying the thromboemblism issue. In essence, he asked that we turn the drug down outright if we felt the available data could not justify a favorable benefit/risk decision in regard to marketing. . . . Our view was that we could not discuss with any seriousness the issue of approval for marketing unless the labeling included a strong warning about thromboembolic risk. While the possibility still existed that this apparent risk was related to the disease psoriasis and not to the drug, the more conservative, and in our view more likely, assumption was that the risk was real and drug-related. We agreed to present the matter again to our advisors on condition the firm submit labeling which reflected current best estimates of the thomboembolic risk and a protocol for a phase IV study.

On February 26, 1974, the FDA met with an advisory committee of statistical and epidemiological experts—the Biometric and Epidemiological Advisory Committee (BEMAC). This committee endorsed Stolley's conclusion that additional studies should be done in phase III rather then in phase IV—an "option," said Crout, "which was increasingly appearing impractical for the reasons I have described. We may have been remiss in not apprising the BEMAC Committee of the changes in the situation and in our thinking since Dr. Stolley's review. This was an unintended oversight which we regret."

The next day they met with the Dermatology Advisory Committee, which now had several new members. Also present were Stolley and Dr. Samuel Greenhouse, chairman of BEMAC. The committee members voted four to one to recommend approval of the drug on the condition that the indications for use be very limited, that the labeling include

warnings and information about thromboembolism, and that a phase IV study be conducted. One of the consultants to the committee expressed disapproval, but the consultants did not vote.

The FDA review and supervisory team that handled Triazure had also approved of marketing it contingent on a phase IV study, Crout explained. Still,

> I would emphasize that the decision to permit the marketing of Triazure was one of the most difficult we have faced in recent years in the Bureau of Drugs. A close benefit/risk decision always brings out, of course, the range of value judgments which can occur among reasonable persons. At the one end of the spectrum in this case were the drug firm and a number of its consultants arguing that the alleged risk of thromboembolism was not scientifically proven and that, in any event, the important benefit of Triazure to disfigured and crippled psoriatic patients was clearly worth this risk. At the other end of the spectrum tended to be our biostatistical and epidemiological consultants who were most concerned about risk and least impressed with the seriousness of psoriasis. Our dermatologic advisors, in general, fell between these extremes. Somewhere along this spectrum of value judgments each of us involved with Triazure found a resting place, but no consensus decision on this drug was possible.

As for the weight the FDA gave to the difference of opinion between BEMAC and the Dermatology Advisory Committee, Crout explained that it is the policy of the Bureau of Drugs to formally refer benefit/risk issues only to "those advisory committees constituted with medical experts experienced in the use of drugs and in the evaluation of the range of scientific evidence available on a particular drug." The Dermatology Committee was in this category.

Triazure went on the market in Agust 1975. Subsequent to this, Parke, Davis & Company, the large pharmaceutical firm, purchased the drug from Calbiochem and became the distributor.

In August of 1976 the FDA ordered the drug recalled.

One patient had died since marketing, another had had a limb amputated, and six others had developed blood clots subsequent to treatment with Triazure.

Nevertheless, as Crout told the subcommittee,

> The benefit/risk decision to withdraw the drug at this time was also a difficult one. There was every evidence that the drug was in fact being administered quite cautiously by the medical profession to a limited number of patients, since total distribution in the first year was sufficient to treat only 500 to 1,000 people. There was every reason to believe, furthermore, that patients willing to put up with the sometimes distressing, although reversible, gastrointestinal and central nervous system side effects of the drug, its high cost ($7.00 to $10.00 a day), and the risk of thromboembolism were indeed benefiting from the treatment. On the other hand, the severe and unusual nature of the arterial thromboses being reported was a qualitatively new dimension to the thromboembolism problem. Finally, the fact was also considered that a new treatment for severe psoriasis

involving a drug called Methoxsalen and irradiation with high-intensity ultraviolet light is showing considerable promise of being safer than either methotrexate or Triazure. Thus, the role of Triazure as the sole approved alternative to methotrexate may well be changed substantially in the near future. For these several reasons taken together, our medical staff felt that the overall risk/benefit issues with Triazure had changed sufficiently to require immediate withdrawal of the drug from the market.

The FDA, he continued, is permitting Triazure "to be used under its investigational new drug application—IND—on a case-by-case basis in severely disabled psoriatic patients for whom there is no alternative therapy—including methotrexate—who are fully aware of the potential hazards of the drug, and who have accepted this risk. . . . We also will continue to hold open an IND for the use of this drug in patients with mycosis fungoides, a rare, chronic, ultimately fatal malignant disease of the skin. Results in inducing remissions in this disease appear promising."

Should Triazure ever have been permitted to be marketed under phase 4? Why had the FDA not "listened" to Stolley's suggestion that a further, premarketing phase III study be conducted? Since a number of patients had suffered thromboembolic episodes before the drug was marketed, why should there be any surprise at the subsequent episodes? These were among the issues that the subcommittee hammered at during the hearing.

"The principal purpose of this hearing," stated the chairman, Representative L. H. Fountain (D., N.C.), in his opening remarks, "is to examine the circumstances under which the Food and Drug Administration approved the new drug Triazure and then, one year later, ordered it removed from the market. As in a number of our past hearings, the subcommitte is concerned by indications that the safety requirements of the law with respect to new drugs are not being adequately enforced, that patients and their physicians are not being adequately protected, and that FDA is not making proper use of outside advisory committees."

Fountain and his aides on the subcommittee have been long-time critics of the FDA. It is unfortunate that they did not summon a balance of "pro" and "con" witnesses; they have raised the suspicion that they weighted the physician-witness list against the FDA.

One of the witnesses was the only member of the Dermatology Advisory Committee who had voted against releasing Triazure. He is Norman E. Levan, who served as chairman of the committee and is professor of medicine and chairman of the Section of Dermatology at the University of Southern California. Dr. Wilma Bergfeld was the only witness from the group of four other dermatologists on the committee who had voted for it. Aside from these witnesses and the FDA staff, the others were Samuel W. Greenhouse, Ph.D., who was chairman of BEMAC at

the time and is chairman of the Department of Statistics at George Washington University; Arnold L. Schroeter, M.D., assistant professor of dermatology at the Mayo Clinic, the consultant to the Dermatology Advisory Committee who had voiced disapproval; and Paul D. Stolley, M.D., the epidemiologist who had recommended a large phase III study and who is now on the staff of the Department of Research Medicine, University of Pennsylvania Medical School.

Bergfeld was the first to give a prepared statement, followed in alphabetical order by Drs. Greenhouse, Levan, Schroeter and Stolley. After showing the slides of psoriatic patients, Bergfeld stated in part,

> We . . . discussed methotrexate as the model and the use of azaribine [Triazure] as compared to the model. We deliberated for some time. . . . There was a disagreement as to the approval or allowance of releasing the drug to the public at that time. However, the committee when voting felt that azaribine was equally effective and equally safe to methotrexate. We felt that . . . if properly labeled . . . and if the particular drug was entered into a phase 4 study that we could . . . ok its usage.
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> Since the release of azaribine we have had in dermatology . . . a third alternate therapy, namely, PUVA, which is the use of oxypsoralen and UVA light. I must say at this time, reflecting on the use of azaribine, and even methotrexate, that both of these drugs are less in usage than they were several years ago and especially 1 year ago. In fact, we are now decreasing our use of both drugs, with the advent of PUVA therapy, which appears to be safer and more effective than both of these therapies. . . .
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> We feel, however, that azaribine should be allowed for treatment of patients—especially those patients we feel may need it, and who are not able to take either methotrexate or PUVA. . . .

Greenhouse, the professor of statistics, noted in his statement that

> unfortunately, one is unable to infer definitely in a rigorous scientific sense that these thromboembolic cases were solely attributable to the drug. The reason for this is that the studies did not contain any control groups. It was thus impossible to compare the frequency of thromboembolism among those treated with Triazure and among those not so treated. As a result, the BEMAC recommended a randomized, controlled clinical trial to resolve the issue. . . . However, I was also aware that the Bureau of Drugs had a most difficult decision to make. In view of clinical needs for what we were told was a very serious, incapacitating disease—some patients under a severe attack talk of suicide—it seems to me the Bureau must consider the implications of depriving these patients of an effective drug, even if the risk were firmly established. . . .
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> In my view, it is the clinician who should advise the agency on risk/benefit ratios once he is informed of the risk involved. The clinician is familiar with the disease and his patients and is best able to decide whether using the drug is worth the risk. In this instance involving Triazure and severe psoriasis, clinicians evidently believed the risk was worth taking. On the other hand, I suppose one could argue that based on Professor Stolley's estimate, a randomized controlled trial would have been able to reach a conclusion within 60 days after all patients had been assigned to either treatment or control, and perhaps the bureau should

have waited. In any event, on behalf of the FDA, I strongly believe that the decision to market, contingent on carrying out a phase IV trial, was not capricious or biased but made in a responsible manner.

Levan, the chairman of the Dermatology Advisory Committee, emphasized that "my opinion is of course on record. It was unequivocal that there was a possible causal relation of the drug to [thromboembolic phenomena] when used in the treatment of patients with psoriasis, that it was significant, and that. . . Triazure should not be released for marketing without further studies." The consultant, Schroeter, stated in part, "It was my opinion that there was significant benefit in the use of azaribine at the recommended dosage for the treatment of psoriasis. All studies have shown amply that azaribine is effective in the control of severe, crippling psoriasis. . . . However, this small psoriatic patient population needing azaribine was not large enough, in my opinion, to justify marketing of this drug. . . . Further, it was realized that those patients in need of azaribine could continue to get the drug at those universities where the phase III studies were in progress."

Stolley related that he had pointed out in a memo before the drug was approved that, of the 556 patients in Calbiochem's files, 23 had,

> developed thromboembolism either while receiving the drug or shortly after having stopped; this came to a rate of approximately four thromboembolism episodes per 100 treated patients. I further noted that . . . two died, which gives a case fatality-rate of nine per 100.
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> Many of the patients, in addition to the psoriasis, had other diseases which may have predisposed them to thromboembolism. However, . . . it was unclear whether "predisposing factors" in the study group of patients . . . were any greater than those which might be found in a control group of a comparably aged population.
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> I suggested . . . that approximately 500 patients with psoriasis be located and matched to the patients who received the drug Triazure on the characteristics of sex, age, and predisposing condition. I then suggested that we follow this control group for the same amount of time that was used to study the psoriatic patients who received the drug Triazure. . . . This would, in a sense, test the claim of Calbiochem that psoriatic patients left untreated would get the same amount of thromboembolism . . . as those psoriatic patients who received the drug. I pointed out that . . . no one would have to be exposed to the drug Triazure in order to answer the question as to whether or not these clotting disorders were drug related.
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> My second conclusion in the memo was that enough was known . . . to suggest that the thromboembolism was related to the drug and not due to coincidence. Finally, I ended the memorandum by stating that if the drug were marketed, it would be quite reasonable to expect the occurrence of a significant frequency of thromboembolism among patients receiving the drug, leading even to disability or to death. I also expressed reservations about the possibility of limiting this probable side effect by means of labeling designed to warn persons with the so-called "predisposing factors" to avoid taking the drug. . . .

During the subsequent questioning of the witness by Chairman Fountain and others, Levan was asked if he agreed with Schroeter on the need for systemic drugs even in severe cases of psoriasis. He replied that "any systemic drug with serious dangers is not an appropriate model for a disease which, in extreme and rare exceptions, is not life threatening." As for "the introduction of the plea that suicide attempts occur I would have to examine each case with the aid of people who know the patient and the circumstances. I find the anecdotal, unexamined information unconvincing. . . . I have seen very many psoriatic patients who lead normal lives in the face of what could bother others." What proportion of patients, Fountain asked, had the type of severe psoriasis that Bergfeld had shown in her slides? Levan replied that his institution, Los Angeles County–USC medical center hospitalized very few, perhaps six each year. Bergfeld, however, countered that in the "experience of the Cleveland Clinic . . . we have allotted to us 40 beds in a 1,000-bed hospital, 25–30 of which always contain psoriatics. So our population group is different, Dr. Levan, than yours; we feel that we have a necessity for good therapies, alternative therapies, in these patients."

Fountain asked Bergfeld, as "one of the majority who voted to recommend approval," what her opinion of Triazure was today in regard to its safety. She replied, "Well, I would qualify my opinion as of today, because 'today' means many things. Today we have much more information available to us and we have another mode of therapy which is preferred. . . ." Two Cleveland Clinic patients had died of Triazure-related complications, but "we are not beyond using it again" if they had a patient refractory to treatment.

She was also asked if at the time she gave her approval to Triazure she was satisfied "that the risks had been sufficiently quantified" to permit her to make a benefit/risk ratio.

She replied that the Advisory Committee was concerned about the risk but felt that "it had to be better defined. We were stuck with the fact, if you can appreciate this, that we were dealing with a model drug called methotrexate, which indeed, had toxicity. We were trying to consider a new drug in comparison to the one we had, which was effective and deemed safe enough. This drug [Triazure] met those qualifications if, and I emphasize *if*, a phase IV or a continued investigation of thromboembolic phenomena was engaged in."

Later, Fountain pressed the same point. "Dr. Bergfeld, refer again to your decision to vote to recommend approval. Do you feel that you had sufficient reliable information concerning the effectiveness of the drug so that a benefit/risk evaluation could be made?"

"Yes," she replied.

Fountain also asked if Bergfeld recalled any "report to the advisory

committee specifically dealing with the sufficiency of the testing data to establish efficacy of the drug by at least 2 adequate, well-controlled studies by qualified experts, which is the requirement of FDA regulations?"

"We have in our folder, which many of us brought today and have reviewed," she answered, "studies which were done at that time. One particularly seems to be of great merit and the others are rather questionable. However, many of us who sat on that committee were already familiar with the drug and with other open studies that were being done. We also had the opportunity to have been at the Academy of Dermatology at which much of this material had been presented . . . so that we were not coming without information. I've also had personal experience. . . . I was aware of good studies, . . . including these that were presented to us and I personally thought that it was an effective therapy and worth the benefit/risk."

Levan, in answer to the same question, stated that there was essentially no discussion of efficacy of Triazure at that session, that "the danger of thromboembolic phenomenon was of such importance that further consideration of efficacy would not have been appropriate until it had been resolved. This danger was convincingly discussed by Drs. Greenhouse, Schroeter, and Stolley, and because of this danger I agreed with them that the marketing of Triazure should not be approved."

Schroeter stressed that the committee's attention had been almost entirely focused upon the risks of the drug. For one thing, the matter of efficacy had been reviewed by the first Dermatology Advisory Committee that had met back on June 11, 1973. For another, articles had been published reviewing the drug's efficacy. And these "appeared to be good," he said. "I think everybody accepted that. The problem here may be that there was a change in the membership" of the Dermatology Advisory Committee since the first meeting. And as a result of that change "there may have been some members who were not completely familiar with that data. However, I question that because this drug had been around for quite some time. . . . The real problem was the risk/benefit ratio."

Did he think they had had enough adequate studies to make a determination? As for efficacy, he said: Yes. As for risk: No.

Later on, a subcommittee aide said, "Dr. Schroeter, in your response to the chairman just a moment ago you emphasized the fact that on some occasions a drug which has a high-risk factor of toxicity would be approved, or should be approved where the disease to be treated was a fatal disease. I take it that you would not put psoriasis in that category?"

"This is a judgmental thing. It is an opinion." Schroeter replied. "I am sure my colleagues will vary. . . . Psoriasis is not cancer, although it proliferates . . . and the patient in terms of his own subjective experience

may rather have cancer, but this is not cancer. Nevertheless, I qualify that and say that there are a very small percentage of patients who do have a variety of psoriasis which is lethal. . . ."

AIDE: "In your opinion, when the decision is based on an evaluation of risks and benefits, a greater degree of risk will be acceptable where there are clearly fatal diseases involved than where there are arguably fatal or nonfatal diseases involved; is that correct?"

SCHROETER: "I think that is a generalization that you can assume, but in application it becomes very difficult. Theoretically that sounds good but practicably it is very difficult."

AIDE: "Is it your understanding . . . that in determining whether a new drug can be marketed commercially, that a risk/benefit determination is an appropriate determination . . . is one that can be taken into account under the law?"

SCHROETER: "It is one that has to be taken into account, whether we have a law or not."

What about the fact that FDA files indicated that 20 percent of psoriatics may respond favorably to placebos? Schroeter answered that "I don't think I would question it . . ."; Levan that he "would expect, from the way you worded that question, that at least 20 percent can be expected to react favorably with or without placebo . . ."; and Bergfeld that ". . . the very severe psoriatic generally does not sporadically get better. It is true, however, that . . . certain psoriatics of mild severity and amount will undergo a natural regression or remission of their disease."

Another question Schroeter was asked was whether it was true that, once a drug is put on the market, a physician can use it, regardless of the labeling, for whatever purpose he thinks will help his patient. Schroeter agreed this was true, but he went on to say that "I think we belie the intelligence of the physician here. I think most physicians are leery of these drugs and would rely on the specialty group which is most familiar with the disease and the drug. It is a possibility, but obviously they are liable if they misuse the drug."

After a recess, Crout and other members of the FDA staff who had handled the Triazure application were called to the stand. Following Crout's prepared statement, Fountain and his aides focused a good part of their questioning on the earlier history—that the FDA had twice disapproved the drug, the second time on the advice of the Dermatology Advisory Committee in June 1973, before approving it with the recommendation of the second Dermatology Advisory Committee that had met in 1974. Fountain referred to a January 1973 memo that Crout had sent to Dr. John Saunders, medical officer of the FDA's Division of Anti-infective Drug Products, in which Crout asked him to develop a labeling which would be appropriate for the drug and suggested that approval should be contingent upon a phase IV study by the firm.

FOUNTAIN: "Then you request the [first] Dermatology Advisory Committee to see the data on the drug and to concur on the labeling, the objectives of the phase IV study, and decision for marketing. From your memorandum . . . it would appear that you had made up your mind that FDA move the NDA [new drug application] for approval with phase IV study. But in June 1973 the Dermatology Advisory Committee did not give you the support you were looking for. . . . Isn't that right?"

CROUT: "They did not concur in this approach; that is correct."

FOUNTAIN: "Were the additional phase III studies recommended by the advisory committee . . . performed?"

CROUT: "No."

FOUNTAIN: "Why not?"

CROUT: "The basic thing that happened after the first advisory committee meeting is this. No. 1, new information came in on 179 new patients. That was reviewed with essentially the same findings in regard to thromboembolism as had been found in the previous review of the smaller series of 377 patients. So, new data were showing thromboembolism still to be occurring. No. 2, as I pointed out, the firm made it clear they were not going to do a phase III trial and asked us for a decision on the basis of the data at hand. No. 3, we came to agree with them that the conduct of a controlled trial aimed at merely cementing the level of scientific proof, this incidence of thromboembolism, was not necessary for a judgment on the drug. We could take the data already in hand and accept that as very good evidence of the fact that the drug produced thromboembolism. We could accept this as highly probable, and we could use the data in hand as the data base for decision making."

Was it customary, Fountain wondered, for the FDA to request a company to do extra work—in this case, to pursue further phase III studies—and then go along with their decision not to do it? "Customary" was not the right word, Crout replied, but if you are presented with a reasonable argument as to why your request was either unnecessary or wrong you should change your mind. "Let me amplify that," added a member of his staff. "The material that was submitted in the interim was germane to the request that the Bureau had made . . . for the conduct of additional phase III trials. . . . The new data, on 179 patients . . . provided some confirmatory evidence, if you will, that the original statistics before the agency were probably a pretty good guide as to the likely incidence of those thromboembolic events. The agency's decision to change its mind . . . about the need for additional studies was made in light of this change in circumstance that went to the very issue the agency was concerned about."

They had not followed Stolley's recommendation to conduct a controlled study of 500 patients in a phase III program, Crout said, because they did not feel it was necessary to prove the risk of thromboembolism

because this already looked highly probable to them. And the labeling of the drug would warn about it. Although the pharmaceutical firm, Calbiochem, could not afford further phase III testing and wanted a decision based on the present data, Crout felt that they did want a postmarketing study in the hope of proving that the risk was *not* drug related. He stated that his impression of the position that Calbiochem's president took "was as follows: . . . 'We are a small firm, our resources are becoming exhausted over this, or could be. We would like to be able to answer all of the questions that you and all of our consultants can think up. I am getting a little dismayed with all the scientists who can think of more things than I can pay for. From my point of view, if I finance a phase III trial, and see 3 more years go by, and the data come out the same way they are coming out now, are you going to turn my drug down then? If that is what you think, then tell me now.' I found that to be a reasonable request. . . ."

One of the things Fountain brought up was the memorandum that Stolley had written on October 12, 1973, to a member of the FDA staff. He quoted from it. "I know of no way to write a label that will protect patients with 'predisposing factors' from this risk by warning them away from the drug. There is too little evidence to give any assurance that even if these warnings were observed, the patients would not be at risk of TE [thromboembolism] from the drug, even in the absence of these 'predisposing factors.' "

FOUNTAIN: "Dr. Stolley goes on to say . . . that it would be reasonable to expect 'a significant frequency of TE [thromboembolism] among patients receiving the drug, some of which may lead to disability or death' if the drug were approved on the basis of the available data.' " [To Crout] Were you impressed with Dr. Stolley's analysis?"

CROUT: "Oh yes."

FOUNTAIN: "How much weight did you give it?"

CROUT: "His analysis of the data is absolutely correct. These are the numbers which, in large part, later appeared in the labeling for this drug. I was impressed with, as I am sure we all were, . . . his value judgment that in his view this risk is too great for marketing this drug. I believe, though, that I was ultimately more impressed by the dermatologists, faced with the problem of patient care in this area, who knowingly said, 'Even with these risks we believe the drug should be marketed because of the nature of the condition and severity of the disease.' "

FOUNTAIN: "Is Dr. Stolley a recognized authority in the field of epidemiology?" Absolutely, Crout agreed. But "his value judgment on whether a label could be written, however, is not in the field of epidemiology," he said.

Fountain wondered what facts could be collected in a phase IV study

that could not be obtained in a phase III study without exposing the public to unnecessary risk. "When phrased that way," Crout answered, "there is nothing that can't be required during the premarketing phases. There is no limit to what can be required in premarketing. I think the issue is: Does one at a certain point have to make a reasonable judgment, on the data before him, that a drug is approvable or not? . . . It is always possible to get more and more premarketing. In fact, this is one of the hard things about life in the FDA. You always think of more and more information you would like to have before you reach that moment of truth and make a decision."

Crout was asked if he would have approved the marketing of Triazure if he had had the data that were eventually provided by phase IV. His answer: No. Why? Although the incidence of thromboembolism was perhaps less than the 3 percent that went on the labeling as a warning, the FDA started "getting reports," he said,

> of arterial thrombosis of a character more severe and more alarming than we were getting at the premarketing stage. As I pointed out, premarketing, there were 23 cases of thromboembolic episodes, but half were rather minor episodes in the veins of the legs. Several others were rather common kinds of events like heart attacks in patients who appeared to have predispositions for that. Postmarketing, 7 of the 8 reported events were arterial thromboses in unusual sites, such as in the arm or the toe. There was 1 stroke. There was 1 severe heart attack. There was 1 death from pulmonary embolism. So, the real question scientifically, in my mind, is why weren't those picked up during the investigational phases of the drug? That is an interesting scientific question. I don't know exactly why. But I would emphasize strongly that the character of events changed. The second thing that changed is the need for the drug as an alternative for methotrexate. That need is rapidly going away. This new PUVA treatment is a very important development in the last year.

Crout went on to say, later, that he would like to put

> a different construct on the record . . . and let everyone read and judge for himself. I think the FDA was faced with an effective drug for a small group of patients, which in the course of its development was found to have a kind of hazard which was not anticipated when the trials were designed. Therefore you have to make do with the data you have on hand. There were no control groups aimed at the issue of determining a risk of thromboembolism. That was considered in great detail by the staff and by the consultants, and the general FDA staff judgment was, in spite of this risk, it should be made available for the small group of patients for whom it was indicated. That view was put before an advisory committee, and they said, "Not yet."
>
> We accepted that recommendation. In the course of attempting to implement their recommendation for a controlled trial, it became clear that the firm wouldn't accept this. . . . So, we considered it again, among ourselves and, also, with an advisory committee, which agreed, then, with the marketing under a whole set of conditions attached to the drug, one of which was a phase IV trial. The drug was then approved. . . . the drug was marketed. Within a year two

important things changed. One was . . . the medical need, the other was that the adverse effects . . . that appeared very infrequent at the beginning . . . were becoming more and more frequent.

In his concluding statement, Fountain charged, "I know it's not FDA's intent . . . nevertheless I think the manner in which Triazure has been regulated would make it appear to some people that protection of the patient is not FDA's primary concern. . . . This, I fear, is simply gambling with the public health—a form of Russian Roulette. . . ."

To which Crout replied: "I would like the record to show that I express my profound disagreement with your analysis at the end. I hope it does not reflect any inattentiveness to the testimony laid before you. . . ."

And thus the hearing ended. No patient who had taken Triazure was ever called. Nor were several physicians who wanted to speak on behalf of the release of the drug. One was Leon I. Goldberg, M.D., Ph.D., professor of medicine and pharmacology at the University of Chicago, and chairman, Committee on Clinical Pharmacology, who had been asked to testify by Dr. Ray Gifford, president of the American Society for Clinical Pharmacology and Experimental Therapeutics. His prepared statement, which he never had the opportunity to give, said in part:

I feel very strongly that the decision to release this drug with a very strong warning and under the conditions of continuing phase IV investigations was not only proper but totally appropriate on a risk/benefit basis. I was asked to review the episodes of thromboembolic disease which were reported during the clinical trials of this drug and I would like to present to you my reasoning for supporting the release of this drug with appropriate warning. . . . Many of these patients go from doctor to doctor to seek a drug which will relieve their condition. . . . The possibility, as I saw it at the time of my review, was that patients who were treated by methotrexate and developed premonitory signs of liver disease, would seek [it] from another physician if the drug was stopped by the doctor initially prescribing it. Imagine the impact on a patient whose psoriasis is treated by methotrexate after being told to stop the only effective drug he's ever had. Psychiatrists have told me that such patients are terribly depressed and suicide is a persistent risk. Thus, the Food and Drug Administration had to make the best risk/benefit decision concerning release of a new drug with a possible, but not proven, adverse effect related to increased clotting, with knowledge that the only alternative drug available produces liver disease and other severe adverse reactions.

I would like now to present to you my analysis of the thromboembolic data reported to occur with azaribine and ask you to consider whether there was any other compassionate decision the Food and Drug Administration could have made for this relatively small number of unfortunate patients.

1. If patients are discounted who had predisposing conditions, the incidence of thromboembolic disease would probably not be higher than that in an equal number of untreated psoriatic patients of the same age group. Of the 20 cases of thromboembolic disease, 15 episodes occurred in patients with known predisposing disease or previous thromboembolic episodes. . . .

I could not find a common factor in the clinical laboratory data or in the pathology of the patients to support a drug-associated etiology. My inability to find such a factor, of course, does not prove that such a relationship does not exist. . . .

2. Since the incidence of thromboembolism without predisposing cause is low, a very large number of patients would be required to clearly demonstrate a significant relationship of azaribine administration to thromboembolic disease. The possibility of an increased incidence of thromboembolism in untreated psoriatics would tend to make such a study even more difficult. . . . Such a study would entail a tremendous cooperative effort and a prolonged period of investigation.

3. It has been suggested that further studies should be carried out because of insufficient clinical evidence on which a judgment could be made on the basis of risk/benefit ratio. I would now like to discuss this proposition:

First, there appears to be no question that azaribine is an effective agent for severe psoriasis. . . . The risk component of the formula must be evaluated in the milieu in which the drug will be used. . . . Ultimately, many [patients] are treated with methotrexate which appears to be more dangerous than azaribine, especially with regard to hepatic toxicity. The ethical question in my opinion then is as follows: Are these patients at greater risk if azaribine is not made available? . . . Furthermore, at present, there is no effective threapy for patients with refractory psoriasis who have already sustained liver toxicity to methotrexate, or who have hepatic or renal disease, or other conditions in which methotrexate is contraindicated. Under these circumstances, extending phase III investigations until a relationship between azaribine and thromboembolism is ruled out could do more harm than good. . . .

4. If the above argument is correct, azaribine should be made available for the use of dermatologists as soon as possible. . . .

5. Finally, I recommend that azaribine should continue to be evaluated in phase IV. . . .

It is of interest that no cases of thromboembolism have been reported in nonpsoriatic patients (such as those suffering from mycosis fungoides or polycythemia) treated with Triazure.

Another physician who had asked to be called as a witness is Charles J. McDonald, M.D., professor and head of dermatology at Brown University and head of the Division of Dermatology at Roger Williams General Hospital. He wrote this in a private communication:

Since 1963, Dr. Paul Calabresi and I have invested a considerable amount of time engaged in extensive laboratory and clinical investigations of the drug Triazure. I do not believe there are any investigators whose experience with this drug is more extensive than ours. In our studies we have found the drug to be effective in the following diseases: psoriasis, mycosis fungoides, lymphoma, polycythemia vera, and several solid tumors (when used in combination chemotherapy).

We were shocked and dismayed by the August decision of the Food and Drug Administration to withdraw the drug Triazure from the market. In spite of this action, informal postrecall discussions led us to believe that the Food and Drug Administration was sincerely and in good faith willing to take appropriate steps to rectify an acknowledged bad decision. However, the Fountain Committee

hearings "laid dead" any subsequent positive action by the FDA regarding re-release of Triazure.

In reference to the Fountain Committee hearings, which I did attend as an uninvited spectator, I left the hearing that evening in a very depressed state of mind. I felt then and now that if the committee's activities were representative of those of other congressional committees our democratic governmental process is constantly violated and is in actuality nonexistent. You are correct in your assumption that the panel of physicians who were summoned to appear before the committee was heavily skewed towards those who had previously recommended disapproval of Triazure. . . .

When its administrators were informed of the pending Fountain Committee hearing on Triazure, the Food and Drug Administration made a request to the committee that I be allowed to testify on its behalf. This request was denied. The Calbiochem Company[1] . . . as well as Dr. Calabresi and I, made similar requests. They were also denied.

[As to] the availability of patients who are willing to take the drug in spite of full knowledge of the risks involved . . . there are many such patients. For example, we experienced no difficulty in recuiting patients for our phase IV study in spite of our having to explain to each patient in great detail (informed consent) that the purpose of the study was to evaluate the extent, if any, of the thromboembolic problem in psoriatics given Triazure.

I cannot at this time give you an exact number of patients or a percentage of patients who will still elect to use Triazure. However, of approximately 40 patients of mine on Triazure at the time of its recall, only one returned a supply of drugs as requested. All others who have had drug available have continued to take it until their supplies are exhausted. Those patients whose disease has exacerbated off drug have all requested to be placed on drug (Triazure) again. This includes one patient who has had about 20 of the new PUVA treatments. A number of these patients are very irate because they have been on Triazure continuously for up to 12 years without experiencing any difficulties. . . .

In summary, Triazure was—and is—an effective drug for a potentially lethal disease. The only alternative on the market for crippling psoriasis—methotrexate—is a highly toxic anticancer drug that can cause serious side effects, including death. The promising new therapy—methoxsalen plus UV light—is still experimental and will, in any case, not work in some patients who *do* respond to Triazure.

The estimates made, prior to marketing, of risk of thromboembolism have held up, although there has been a shift in the direction of more arterial and fewer venous thromboses. There are *still* no good data on how many of these events are related to the disease as opposed to the treatment. Even if the most pessimistic estimates are true, and all the trouble seen *is* due to the drug, there are experienced dermatologists and pitifully sick patients who consider the risks worth taking. There is no evidence that the drug was promiscuously used for trivial disease. The manufacturer almost certainly would never make enough in sales to

[1]In fact, Calbiochem did not request that it be allowed to testify, believing that expert scientists like Goldberg and McDonald were more appropriate witnesses.

pay for the drug's development costs even if the drug were kept on the market—but now Parke Davis is asked to continue to make Triazure available to patients and doctors on a gratuitous basis.

The whole incident appears to exemplify the judicious use of advisory committees and a courageous and wise decision on the part of the Bureau of Drugs to allow marketing. One can, however, question the defensibility of the subsequent withdrawal, despite the advent of a newer (and as yet unapproved) remedy which seems devoid of impact on the severe psoriatic arthritis of certain patients.

There are, to be sure, few patients with such severe disease that they are candidates for Triazure therapy, but are they to be made therapeutic orphans because of their small numbers? Is the Triazure story one that will encourage any manufacturer to invest money in developing a drug that will never be profitable? Must our drug regulatory decisions be determined by those who err on the side of therapeutic nihilism? Why are experts in one field (epidemiology, e.g.) given credence when they express opinions on the treatment of patients about which they have not had the slightest experience? How can one insure that knowledgeable experts who have views opposite to those of a congressional committee staff have a chance to testify?

So, though the episode seems over, the questions it has provoked linger on. Though the congressional hearing on Triazure lasted but 1 day, its potentially devastating repercussions upon the quality of health care in this country will last as long as the issues go unrecognized or, perhaps worse, are ignored.

### *DEATH, BE NOT IMMINENT*

Death, be not imminent,
tarry, tarry yet a while,
come then stealthily,
seduce, persuade by guile.

Be not importunate,
restrain impatient haste;
who other than yourself
has eternity to waste?

SAMUEL STEARNS

# THE DRUG LAG REVISITED: COMPARISON BY THERAPEUTIC AREA OF PATTERNS OF DRUGS MARKETED IN THE UNITED STATES AND GREAT BRITAIN FROM 1972 THROUGH 1976

WILLIAM M. WARDELL, M.D., PH.D.
Rochester, N. Y.

Center for the Study of Drug Development, Departments of Pharmacology and Toxicology and of Medicine, University of Rochester Medical Center

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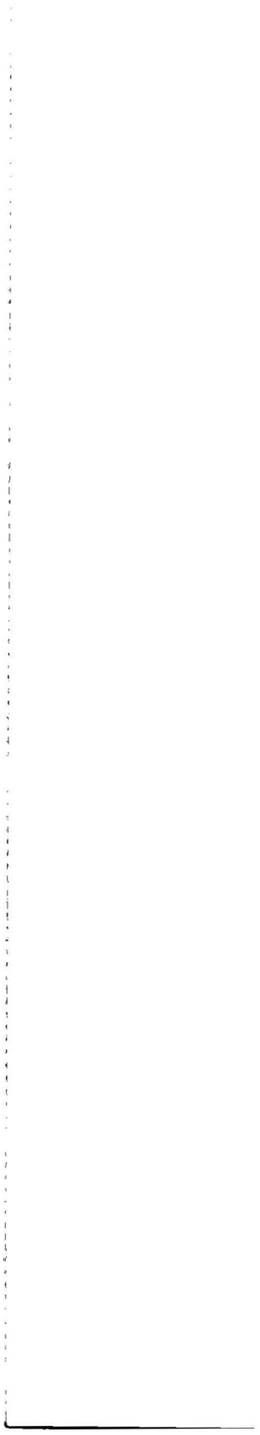

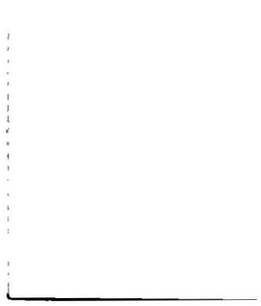

## Original articles

# The drug lag revisited: Comparison by therapeutic area of patterns of drugs marketed in the United States and Great Britain from 1972 through 1976*†

*This study describes rates and patterns of new drug introductions in the U.S. and Britain from January, 1972, through December, 1976, updating an earlier study that described the patterns over the previous decade. This comparative international approach enables overall effects of different regulatory, industrial, and other types of changes in drug research and development in the two countries to be evaluated. Numerical differences persisted. In the 1972 to 1976 period, 82 new drugs appeared for the first time in either country. Only 29% of these became mutually available in both countries, 2.4 times as many becoming available first in Britain as in the U.S. Of the 71% that became exclusively available, 2.6 times as many became available in Britain as in the U.S. More important than numerical data are clinical implications of differences between the countries. The largest differences have narrowed since the previous study, but important categories in which the U.S. still lagged behind Britain in December, 1976, included cardiovascular drugs, peptic ulcer drugs, and central nervous system drugs–including therapies for depression, epilepsy, and migraine. Several factors contributed to the narrowing of U.S.–British therapeutic differences, including more realistic regulatory practices and higher quality clinical studies in the U.S., more conservative practices in Britain, attention drawn by previous studies to anachronisms in the U.S., and industrial changes such as more efficient penetration of the U.S. market by foreign firms. It is difficult to determine the relative contribution of each of these factors to the narrowing of the international difference.*

**William M. Wardell, M.D., Ph.D.** *Rochester, N. Y.*
*Center for the Study of Drug Development, Departments of Pharmacology and Toxicology and of Medicine, University of Rochester Medical Center*

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Reprint requests to: William M. Wardell, M.D., Ph.D., Department of Pharmacology, University of Rochester Medical Center, 601 Elmwood Ave., Rochester, NY 14642.

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†A preliminary study of the changes from 1972 through mid-1974 is contained in Wardell, W. M.: Developments since 1971 in the patterns of introduction of new therapeutic drugs in the United States and Britain, *in* Helms, R. B., editor: Drug development and marketing, Washington, D. C., American Enterprise Institute for Public Policy Research, 1975, pp. 165-181.

As a measure of pharmaceutical innovation, information on new chemical entities (NCEs) that reach the point of marketing represents the ultimate expression of the several major influences (notably industrial and regulatory factors) that are involved in the process of drug development.

In 1972, we examined the pattern of introduction of new therapeutic drugs in the United States over the decade that had elapsed since the passage of the Kefauver-Harris drug amendments, and compared this pattern with the cor-

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**Table I.** *Summary of new drug introductions in Great Britain and the United States from January, 1972, through December, 1976**

| | | | Mutual | | | | |
|---|---|---|---|---|---|---|---|
| | | | *Britain first* | | *U.S. first* | | *Total mutual drugs* |
| | | *Total* | *Drugs* | *Months*† | *Drugs* | *Months*† | |
| Cardiovascular | (15) | 16 | 2 | 14 | 1 | 27 | 3 |
| Diuretic | (10) | 2 | 1 | 18 | — | — | 1 |
| Respiratory | (8) | 2 | 1 | 42 | — | — | 1 |
| Anti-infective | (47) | 18 | 5 | 19 | 4 | 11.3 | 9 |
| Anticancer | (17) | 6 | 1 | 10 | 1 | 5 | 2 |
| CNS | (36) | 23 | 4 | 10.8 | 1 | 8 | 5 |
| Anesthetic | (10) | 4 | — | — | — | — | — |
| Analgesic | (8) | 8 | 2 | 30.5 | — | — | 2 |
| Gastrointestinal | (7) | 3 | 1 | 19 | — | — | 1 |
| Total | (158) | 82 | 17 | 316 | 7 | 85 | 24 |
| Average | | | | 18.6 | | 12.2 | |
| | | | (32) | | (19) | | (65)‡ |

*Drugs available in either country before 1972 are excluded. The corresponding values for the previous decade are shown in parentheses.
†The mean is given where more than one drug is involved.
‡Fourteen new drugs were introduced in both countries during the same year and were considered to be simultaneous in the previous analysis.

**Table II.** *Summary of new drug introductions in either Britain or the United States from January, 1972, through December, 1976**

| | | Mutual | | | | |
|---|---|---|---|---|---|---|
| | | *Britain first* | | *U.S. first* | | *Total mutual drugs* |
| | *Total*† | *Drugs* | *Months*‡ | *Drugs* | *Months*‡ | |
| Cardiovascular | 17 | 3 | 23.3 | 1 | 27 | 4 |
| Diuretic | 2 | 1 | 18 | — | — | 1 |
| Respiratory | 5 | 4 | 65.5 | — | — | 4 |
| Anti-infective | 21 | 6 | 25.3 | 6 | 12.2 | 12 |
| Anticancer | 9 | 2 | 21.5 | 3 | 32.7 | 5 |
| CNS | 25 | 5 | 31.8 | 2 | 25 | 7 |
| Anesthetic | 6 | 2 | 52 | — | — | 2 |
| Analgesic | 10 | 3 | 42.7 | 1 | 27 | 4 |
| Gastrointestinal | 5 | 3 | 62.7 | — | — | 3 |
| Total | 100 | 29 | 112.4 | 13 | 275 | 42 |
| Average | | | 38.8 | | 21.2 | |

*Drugs previously available in other country before 1972 are included.
†The total includes the exclusively available drugs listed in Table I.
‡The mean is given where more than one drug is involved.

responding pattern in Britain for the same period.[25, 27] In that study, a considerable difference was found in the number and patterns of NCEs marketed in the U.S. and Britain, and clear-cut therapeutic implications of these differences were apparent. British usage and American awareness of some new therapeutic drugs were surveyed in five therapeutic areas[22] and the implications of the observed substantial international differences in the availability, use, and knowledge of new therapies were analyzed to determine whether, in therapeutic terms, the U.S. had gained or lost from adopting its more stringent regulatory policies. On balance, our conclusion was that Britain appeared to have gained in comparison with the U.S. from its less

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| *Exclusive* | | | | *Total exclusive drugs* |
|---|---|---|---|---|
| *Britain* | | *U.S.* | | |
| *Drugs* | *Months†* | *Drugs* | *Months†* | |
| 13 | 24.1 | — | — | 13 |
| 1 | 42 | — | — | 1 |
| 1 | 30 | — | — | 1 |
| 3 | 24.3 | 6 | 21.2 | 9 |
| 2 | 24 | 2 | 17.5 | 4 |
| 13 | 31.4 | 5 | 26.4 | 18 |
| 2 | 29 | 2 | 28 | 4 |
| 5 | 42 | 1 | 9 | 6 |
| 2 | 25 | — | — | 2 |
| 42 | 123.2 | 16 | 359 | 58 |
| | 29.3 | | 22.4 | |
| (72) | | (21) | | (93) |

restrictive policy toward the marketing of new drugs, coupled with its more developed program of postmarketing surveillance.[28]

This present study extends the same U.S.–British comparison from the beginning of 1972 through the end of 1976 to determine whether any changes have occurred in these 5 years in the pattern of new drug introductions in each country, or in the relationship between them. Identifiable changes in the relationship between the two countries would be of interest, because regulatory approaches in the U.S. and Britain evolved considerably during this period.

In Britain, the Medicines Act (1968) became law in September, 1971. As a result, the review process for new drugs has become more institutionalized, in some respects coming to resemble that of the U.S. In certain respects regulatory control of clinical drug research in Britain has been increasing faster than in the U.S., beginning before the Medicines Act was implemented. The regulatory situation has also become more complex in the U.S. since the early 1970s. In addition to specific and proposed new regulations, several external factors have affected the actions of the FDA's Bureau of Drugs in its review and approval of new drugs. These were well described in the reports of the HEW Review Panel on New Drug Regulation.[10] Thus, in view of the complexity of the influences known to be affecting the process of drug development and approval, the international comparison of drugs reaching the market offers a relatively straightforward way of examining the overall effects of all such factors.

## Methods

The methods used were similar to those in the previous study.[25, 27] As before, the study examines nine major therapeutic areas and deals primarily with new chemical entities, which we define as new molecular structures excluding new salts, esters, dose forms, vaccines, and biologicals. Significant new drugs that fell outside these criteria are referred to in the text or tables but are excluded from the numerical summaries. Thus, although the approval of an existing drug for a new indication may be as important as the availability of a new molecule, new indications are excluded from the numerical summaries (Tables I and II) but are included in the tables and figures for specific therapeutic areas. Each drug is counted only once in the numerical summaries.

The available data sources for Britain primarily cover drugs introduced into general practice; thus, the data will understate the priority of marketing in Britain for those drugs that were introduced earlier in hospitals than in general practice, and may omit certain drugs introduced only into hospitals in Britain. Hence, in the present circumstances, the comparison tends to understate the differences between Britain and the U.S.

Wherever possible, the dates shown are the dates of initial regulatory approval or, where indicated, the date of approval for a specified indication. Such approval dates are available for most U.S. drugs from the FDA, but comparable approval dates are considered confidential by the British government until the drug is marketed. (Most of the approval dates available for Britain were obtained from the Committee on Safety of Medicines.) When publicly available, information was obtained directly from the pharmaceutical company involved. Where subsequent approval dates for different indications are important, these are provided in the tables or text. Where an approval date was not available, the date of marketing was used (obtained from deHaen[5] or MIMS[15] or the firm involved) and a

mid-year date was assumed for the calculations. Thus, the data actually available are usually the date of approval of a drug for marketing in the U.S. and the date of its marketing in Britain. Again this tends to underestimate the difference between Britain and the U.S., so that the overall comparison presented in this study is conservative in that sense.

## Results

The full results are presented in the form of tables, while graphs are used to show when, and for how long, drugs were exclusively available in each country. For every therapeutic category or subcategory, time is represented horizontally in the graphs and a horizontal dashed line bisects the field. Those drugs that were exclusively available in Britain (or, where the information is accurately known, exclusively approved for a particular use there) are shown above this line, and those in the U.S. below the line. The bar representing each drug extends from the time the drug became exclusively available (or its use exclusively approved) until its exclusive availability ceased—usually because the drug was marketed in the other country but occasionally (where noted) because it was withdrawn or restricted.

Thus, a preponderance of bars above the horizontal line indicates a British lead in exclusively available or usable drugs, while a preponderance below the line indicates an American lead. The length of the bar shows how long the disparity persisted. What is important is not only the number of drugs available, but also their identity and pharmacologic and therapeutic significance. The graphic display is the most useful way to organize this information; a vertical line on the graph at any point on the time axis allows one to examine the differences between the range of drugs exclusively available in each country up to and including that time.

***Numerical summary of new drug approvals from January, 1972, through December, 1976.*** The summary data for this 5-year period are shown in Tables I and II. Table I includes the 82 new drugs that appeared for the first time, while Table II includes an additional 18 "catch-up" drugs that had been exclusively available in one of the two countries prior to 1972 and that became available in the other country during the period 1972-1976.

It is instructive first to compare the rate of appearance of new drugs over the recent 5-year period with the corresponding rate of the previous decade. This comparison is best made on the basis of new drugs that appeared for the first time in the period under consideration. For this purpose, Table I of this paper is compared with Table I of Reference 25, with the "catch-up" entries excluded from the latter. (These exclusions reduced the number of drugs in the 1962 to 1971 table from 180 to 158.) The distribution of the 158 drugs for 1962 to 1971 are shown in brackets in Table I of this paper.

The rate of appearance of new drugs has been approximately the same over these 5 years as the previous decade: a total of 82 new drugs appeared in the 5 years (compared with 158 in the previous 10 years); 24 became mutually available (compared with 65), while 58 became exclusively available (compared with 93).

The large numerical differences in patterns between Britain and the U.S. continued or tended to increase. Considering first only those drugs that appeared after 1971 (Table I), only 29% of the drugs became mutually available in both countries (compared with 41%), of which 2.4 times as many became available first in Britain than became available first in the U.S. (compared with 1.7 times as many). Seventy-one percent of the drugs became exclusively available in one of the two countries (compared with 59%). Of these, 2.6 times as many became exclusively available in Britain as in the U.S. (compared with 3.4 times as many).

Alternatively, 42 drugs that had been available in either country during the 1972 to 1976 period or prior to 1972 were introduced into the other country between 1972 and 1976 (Table II). Of these drugs, 29 were introduced first in Britain, and 13 were introduced first in the U.S. The average lead time for drugs appearing first in Britain was 38.1 months (range, 4 to 133 months), while the average lead time for those appearing first in the U.S. was 24.8 months (range, 5 to 71 months). Expressed as a single index, among those drugs that became mutually available there were 23 "drug years" of prior availability in the U.S., while the correspond-

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**Table III.** *Introduction of cardiovascular drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *Antihypertensives* | | | | |
| β-Blockers †‡ | 2/69 | 5/76 | 85 | |
| Clonidine (Catapres) | 3/71m | 9/74 | 42 | |
| Diazoxide (Eudemine, U.K.; Hyperstat, U.S.) | ?/72m§ | 1/73 | (7) | |
| Prazosin (Sinetens, Hypovase, U.K.; Minipres, U.S.) | 9/74m | 6/76 | 21 | |
| *β-Adrenoreceptor antagonists* | | | | |
| Sotalol (Beta-Cardone, Sotacor) | 6/74m | — | | |
| Timolol (Blocadren) | 6/74m | — | | |
| Pindolol (Visken) | 10/74m | — | | |
| Acebutolol (Sectral) | 4/75m | — | | |
| Metoprolol (Betaloc, Lopresor) | 7/75m | — | | |
| Atenolol (Tenormin) | 7/76m | — | | |
| *Antiarrhythmics* | | | | |
| Disopyramide (Rythmodan) | 6/72 | — | | |
| Phenytoin (Epanutin)† | 8/73m | — | | |
| Mexiletine (Mexitil) | 4/76m | — | | |
| *Others* | | | | |
| Naftidrofuryl (Praxilene) | 1/72 | — | | |
| Dopamine (Intropin) | 5/76m | 2/74 | | 27 |
| Oxypentifylline (Trental) | 10/75m | — | | |
| Perhexiline (Pexid) | 1/76m | — | | |
| Medigoxin (Lanitop) | 4/76m | — | | |
| *Hypolipidemics* | | | | |
| Polidexide (Secholex) | 5/74m | — | | |

*Date of marketing is indicated by "m."

†Listed here but does not satisfy all criteria for inclusion in numerical summaries (Tables I and II).

‡All β-blockers are approved in Britain for use as antihypertensives. The date of first specific approval for this indication in Britain was for propranolol in February, 1969. It was first approved in Britain in 1965. The first U.S. approval for an antihypertensive action of a β-blocker was for propranolol in May, 1976. It was first approved in the U.S. in November, 1967.

§In the case of hospital use, diazoxide was available earlier than this in Britain. The month of marketing was unavailable so the calculation of the lead was based on a June date.

ing figure for Britain (94 drug years) was 4.1 times as many (Table II).

***Cardiovascular drugs.*** In the original study,[25, 27] the cardiovascular area was identified as one in which particularly large differences had arisen between Britain and the U.S. These numerical differences persisted, as seen from Table I where 13 of the 16 new drugs to appear in this category were introduced exclusively in Britain.

*Antihypertensives.* As seen in Table III and Fig. 1, no antihypertensive drugs were approved in the U.S. for the entire decade, i.e., from the introduction of pargyline and methyldopa in 1963 to the introduction of diazoxide in 1973; by contrast, new antihypertensive drugs continued to appear in Britain. Large differences between the two countries arose in all the major classes of antihypertensive drugs except diuretics. Several β-blockers were well established as major antihypertensive drugs in Britain, propranolol having been approved for this purpose in 1969, whereas the only member of this class available in the U.S. (propranolol) was not approved as an antihypertensive until 1976. Adrenergic-neurone–blocking drugs were used much more extensively abroad than in the U.S., due at least in part to the availability of more convenient members of this class abroad,[16] and other drugs, such as clonidine and

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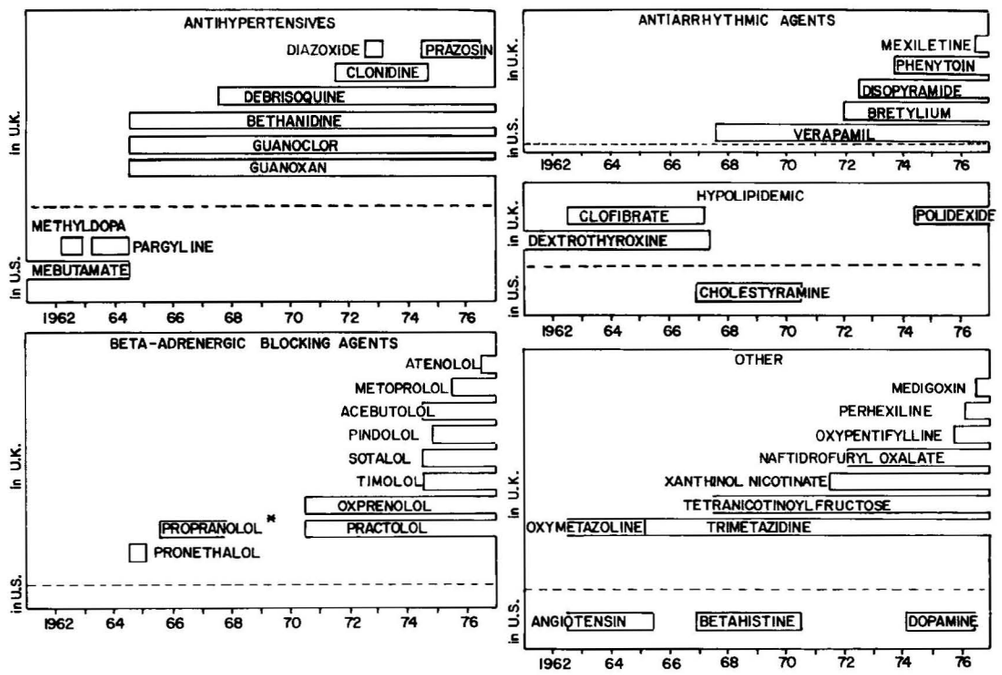


**Fig. 1.** Exclusive availability of cardiovascular drugs. *This drug was available only for restricted indications in the U.S. See text for details.

diazoxide, were valuable alternatives to existing therapy.

In a recent study[16] we explored some of the differences in usage that arose between the U.S. and three other countries (Britain, Australia, and New Zealand) as a result of differences in patterns of availability. We used the national consumption statistics from each country to compute the number of defined daily doses per thousand of population per year (DDD/1,000) for each drug. These values were used to compare per capita consumption of antihypertensive drugs in the four countries. One of the striking differences in usage patterns was the heavy reliance in the U.S. on the older drugs such as rauwolfia alkaloids. On a per capita basis, the consumption of rauwolfia alkaloids in the U.S. by 1972 was more than four times the rate in Britain, and even double the rate in Australia, despite the fact that the total rate of usage of nondiuretic antihypertensives (NDAH) in Australia was considerably higher than in the U.S. On a percentage basis, rauwolfia alkaloids accounted for 75% of the total U.S. NDAH use, while in Britain the fraction was 23%, i.e., less than a third of the U.S. fraction.

Conversely, the use of adrenergic-neurone–blocking drugs was much higher in the other countries than in the U.S. On a per capita basis, the use of these drugs was nearly four times as great in Britain as in the U.S., and more than 10 times as great in New Zealand as in the U.S.; in the latter comparison, the corresponding fractions of the total NDAH use contributed by adrenergic-neurone–blocking drugs were 38% and 5% respectively, representing nearly an eight-fold difference.

Even within the class of adrenergic-neurone–blocking drugs, some interesting differences appeared between the countries as a result of the differences in drugs available. In the U.S., the only member of this class of drugs is guanethidine, while in the other three countries two additional drugs were available, bethanidine and debrisoquin which together accounted for approximately one third of the total adrenergic-neurone blocker usage in these three countries. Thus, comparing New Zealand with

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the U.S. on a DDD/1,000 basis, New Zealand had more than six times the guanethidine consumption, plus an additional consumption (equivalent to nearly four times the U.S. guanethidine consumption) of adrenergic-neurone–blocking drugs that were not available in the U.S.

The per capita use of methyldopa also showed wide international differences, being lowest in the U.S. and highest (by a factor of 3.4 times) in Australia. In terms of the percentage of methyldopa in relation to total NDAH consumption, the U.S. had the lowest ratio (16%), while Britain had the highest (nearly 50%).

A further large difference could be seen in the use of fixed-combination drugs, namely, NDAH in fixed combinations with (for the most part) diuretics. In the case of rauwolfia alkaloids, for example, there were very wide variations in combination use, with the U.S. being a high user (74% of all rauwolfia DDDs used in the U.S. were in combination) and Australia having essentially no combinations at all. New Zealand and Britain were intermediate with, respectively, one half and one third of rauwolfia use being in fixed combinations.

The dominant position of rauwolfia derivatives as the mainstay of the NDAH class in the U.S. was declining slowly throughout the early 1970s, but this decline accelerated in 1974 when rauwolfia derivatives were linked (probably wrongly, as it now appears) with breast cancer.[1, 2, 9, 17]

During the 5-year period, the largest differences between Britain and the U.S. in this field narrowed with the approval of a β-blocker and clonidine for use in hypertension in the U.S., after lags of 7 and over 3 years, respectively. Newer drugs such as diazoxide and prazosin appeared in the U.S. with lags of 6 months and 2 years, respectively.

There were still effective drugs unavailable in the U.S., including bethanidine and debrisoquine. Since it has been more than 14 years and 10 years since these drugs were introduced in Britain, however, their current importance is less than it was initially due to the steady evolution of antihypertensive therapy as new drugs have been developed. Nevertheless, as shown above, the influence of these drugs abroad has been substantial as evidenced by the different attitudes toward, and place of adrenergic-neurone–blocking drugs in, the therapy of hypertension.

The differences in antihypertensive therapy that arose between Britain and the U.S. as a result of the greater range of drugs available in Britain are illustrated by the following statement from a paper by Turner and his colleagues who, in 1976, reported their experience with antihypertensive drugs over the previous decade. "In the last 10 years significant side effects have ceased to be a problem, a fact which is attributable to not using methyldopa, guanethidine, rauwolfia or clonidine, to using diuretics, hydralazine or bethanidine for special indications, and relying mainly on the adrenergic-blocking drug debrisoquine, and a beta-blocking agent—initially propranolol, but in recent years, oxprenolol."[19]

The β-blockers are considered in detail in the next section. At this point it is sufficient to note that their antihypertensive action is probably the most important therapeutic discovery of the past 15 years for the treatment of hypertension.

In summary, the largest clinically important discrepancies in the availability of antihypertensive drugs between Britain and the U.S. have diminished as the new drugs, together with some of the older ones, have become available in the U.S.—in all cases after delays which for some drugs are of many years duration. There were still several important drugs available abroad that were not available in the U.S. by the end of 1976, and there is a legacy of different patterns of treatment for hypertension that still lingers.

*The β-blockers.* In awarding the 1976 Lasker prize for Clinical Research to Drs. Raymond Ahlquist and James Black, the respective discoverers of β-receptors and the clinical significance of β-blockade, the Lasker jurors described this class of drugs as one of the most important of the century for the treatment of hypertension and heart disease. The β-blockers have been found to be valuable in an increasing range of disease states. However, as has been the case with antihypertensive and antiarrhythmic drugs, there has invariably been a significant time lag between their approval for

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each given indication in Britain and their approval in the U.S. In addition, the number of β-blockers available in the U.S. is still limited to a single drug, while nine were available in Britain by December, 1976.

The one β-blocker that is available in the U.S. is propranolol. Its initial approval in 1968, 3 years after its approval in Britain, was for a very restricted range of indications—namely, certain types of ventricular arrhythmias, idiopathic hypertrophic subaortic stenosis, and pheochromocytoma. Approval for its use in angina was not obtained in the U.S. for another 5 years (1973) and it was finally approved for hypertension in May, 1976. Thus these last two indications were approved in the U.S. 9 and 12 years after the drug's efficacy in these conditions had first been reported in the world's medical literature, and 7 years in each case after the drug was approved in Britain for the same indications.

During the past 10 years there have been several developments in β-blocker pharmacology, leading to a rapid expansion of the number of β-blockers available abroad and raising the important issue of whether those β-blockers that have appeared since the initial members of the series offer any clinical advantages. There are several areas in which the β-blockers differ among themselves to degrees that are already established as clinically useful. The main areas of difference between members of the series are as follows.

1. Pharmacodynamic properties, including cardioselectivity, intrinsic sympathomimetic activity, membrane (antiarrhythmic) activity, and concomitant α-blocking activity. Differences in these properties can offer theoretical or real advantages to some patient populations in terms of differences in the production of asthma and heart failure and differences in hypotensive and antiarrhythmic efficacy. For example, cardioselective compounds such as metoprolol have less tendency to induce bronchospasm in asthmatic patients and so can be used in certain patients in whom propranolol is contraindicated.

2. Pharmacokinetic properties, such as a longer duration of action. Differences in this area permit, with some of the newer β-blockers for example, a less frequent dosing schedule and hence aid patient compliance, an important feature in the control of diseases such as hypertension.

3. Other properties, such as central nervous system (CNS) side effects. Although not yet well characterized in formal clinical trials, there is enough clinical experience to show real differences in CNS actions among different β-blockers; an early case in point was that practolol was a useful alternative for patients who had intolerable depression or nightmares while on propranolol.

Thus, there are rational pharmacologic and clinical grounds for selection among the different β-blockers, but more comparative studies between the different drugs are needed to identify subpopulations for which different drugs are best suited. This will become more necessary as the range of indications and the number of patients who become candidates for treatment with β-blockers increase.

*Antiarrhythmic drugs*. Since 1968, when the β-blockers were approved for use in arrhythmias, through 1976 no new antiarrhythmics were approved in the U.S. Except for lidocaine, the use of which as an antiarrhythmic was belatedly approved in 1970, no other antiarrhythmic drugs or uses were approved since the introduction of procainamide in 1950. There were, however, five antiarrhythmics exclusively available in Britain, three of which appeared in 1972 to 1976.

As of December, 1976, two antiarrhythmics, namely bretylium tosylate and disopyramide, had been exclusively available in Britain since 1972.* These drugs have been found to be effective for certain patients as well as relatively safe and have been found to be useful alternatives to the presently available antiarrhythmics.

The antiarrhythmic effects of both bretylium and disopyramide were actually first discovered in the U.S. more than 10 years ago. The importance of alternatives to the small number of an-

*Bretylium, which was originally marketed in Britain as an antihypertensive in 1959, was approved in Britain as an antiarrhythmic in December, 1971, and marketed for that purpose in November, 1972. It was therefore not included in the previous study and is not included in the tables of the present study.

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**Table IV.** *Introduction of diuretics, slow-release $K^+$, $Na^+$ supplements, and related drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | Britain | U.S. | Britain | U.S. |
| *Diuretics* | | | | |
| Metolazone (Zaroxolyn) | 5/72 | 11/73 | 18 | |
| Bumetanide (Burinex) | 6/73 | — | | |
| *Potassium supplements* | | | | |
| Slow-K† | 8/65m | 4/75 | 116 | |
| *Sodium supplements* | | | | |
| Slow sodium† | 8/72m | — | | |

*Date of marketing is indicated by "m."

†Listed here but does not satisfy all criteria for inclusion in numerical summaries (Tables I and II).

tiarrhythmics presently available in the U.S. is illustrated by the fact that two of the three main drugs currently used in the U.S. (namely, quinidine and procainamide) may induce very troublesome side effects, while lidocaine, the other mainstay of therapy for serious acute ventricular arrhythmias particularly following a myocardial infarction, is well known to be ineffective in some patients.

Two of the remaining antiarrhythmics that are not available in the U.S., verapamil and perhexiline, are also both effective antianginal drugs, and were initially introduced as such.

Verapamil has been exclusively available in Britain since 1967. It has been found to be as effective as the $\beta$-blockers in the symptomatic treatment of angina and has also been found to be very useful in the treatment of supraventricular arrhythmias.

Perhexiline maleate, available in Britain since January, 1976, is a relatively new drug. Its efficacy as an antianginal was first described by Hirshleifer in 1969[12] and since then numerous studies have substantiated this finding. The drug's antiarrhythmic potential was subsequently investigated on the basis of animal and human data which indicated that the drug reduced exercise-induced tachycardia without affecting the resting heart rate. Further studies confirmed perhexiline's antiarrhythmic potential and found it effective, particularly for ventricular arrhythmias. Other actions of perhexiline include a mild diuretic and natriuretic effect. This drug has caused hepatic toxicity in a small proportion of patients.

Mexilitine is a useful new antiarrhythmic that has properties somewhat similar to those of lidocaine, with the additional advantage of being orally active. There is preliminary evidence suggesting that it may reduce postinfarction mortality.

In addition to these several antiarrhythmic drugs that are not available in the U.S., there is one mutually available drug (phenytoin) whose use in arrhythmias is not approved in the U.S. Phenytoin has been found to be effective in some patients in the treatment of digitalis-induced tachyarrhythmias. The drug is extensively used and is recommended by some as the drug of choice in the treatment of these arrhythmias,[29] but has yet to be approved for this indication in the U.S. (NDAs for this indication have been rejected in the U.S. since 1967.)

Considering the number of different etiologies and pathophysiologic mechanisms that induce arrhythmias, it is not surprising that there is no one simple treatment that is consistently effective for arrhythmias. Therefore, the availability of several drugs with differing actions is advantageous in clinical practice to enable treatment to be tailored to each patient, with regard to his arrhythmia, his response to other antiarrhythmic drugs, and his liability to and tolerance of side effects. The ability of the U.S. physician to individualize treatment for arrhythmias compared with his British counter-

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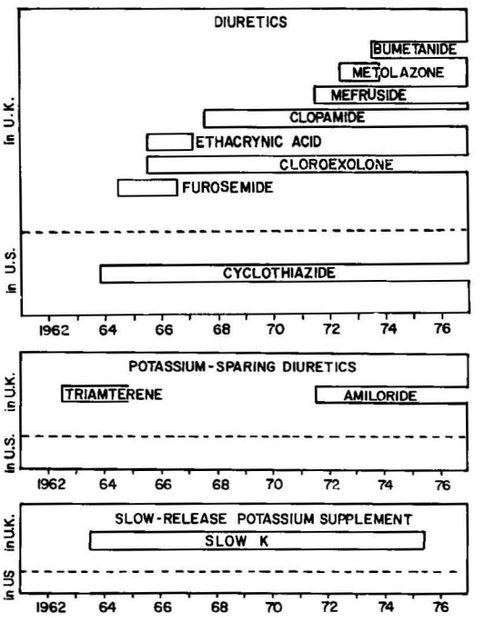


**Fig. 2.** Exclusive availability of diuretics and potassium supplements.

part is noticeably constricted as a result of the smaller number of different drugs available to him.

There is evidence that the narrower range of antiarrhythmic drugs available in the U.S. may have been due, at least in part, to the philosophies of medical reviewing officers in the FDA's Cardiorenal Division. The following passage, which appears as part of a long analysis of the Agency's internal discussions that led to disapprovals of NDAs for phenytoin as an antiarrhythmic from 1967 to 1974 in the FDA's "Commissioner's Report"[18] of October, 1975, is an interesting commentary on the attitudes that prevailed at FDA in the late 1960s toward phenytoin, new antiarrhythmics in general, and practicing physicians.

A physician employed by FDA "expressed dissatisfaction with inadequacies in the medical reports. He also recommended that a new policy be developed to limit the number of anti-arrythmic [sic] drugs on the market. He argued that these agents were complex, unpredictable and paradoxical (i.e., in some circumstances will produce the condition sought to be treated); that there were a variety of agents, ranging from digitalis and quiniline [sic] to beta-blockers to potassium salts, procaine derivatives, and sympathamimetics [sic]"; that "few, if any, physicians are able to be fully knowledgeable concerning the complex pharmacologic variations and characteristics of all these agents"; that unassessable drug effects result if these agents are used concurrently or with other drugs; and that "ideally, a cardiologist should be thoroughly familiar with the characteristics of a minimum of antiarrythmic [sic] agents, such as digitalis, quinidine, and a short acting agent, i.e., lidocaine." He concluded that, although the Federal Food, Drug, and Cosmetic Act does not permit it, he would prefer to require a new product to be proven superior to the digitalis, guinidine [sic], and lidocaine agents before being allowed to market; otherwise, he feared "a 'therapeutic Tower of Babel' which would really increase the dangers to patients."

***Diuretics.*** There were no large clinically important changes in the relative position of each country with respect to diuretics. The strongly potassium-sparing diuretic, amiloride, is still available only in Britain. However, with the introduction of slow-release potassium supplements into the U.S. 12 years after they were introduced in Britain, the overall disparity in this field became smaller than in 1971 (Table IV and Fig. 2).

***Respiratory drugs.*** The bronchoselective $\beta$-adrenergic bronchodilators metaproterenol and terbutaline were approved in the U.S. during the period 1972 to 1976, 11 years and 3 years after their introduction in Britain. This eliminated the clinically important gap that had existed previously in the field of bronchoselective bronchodilators (Table V and Fig. 3).

Two important drugs for asthma, cromolyn sodium and beclomethasone (inhaled), were also introduced in the U.S., after lags of 5 years and 3½ years. This clinically important gap is also closed now, although cromolyn remains exclusively available in Britain for certain other uses (e.g., for nasal insufflation in allergic rhinitis and for allergic conjunctivitis).

The concept of administering steroids as an aerosol is not entirely new, and in fact aerosolization of hydrocortisone, prednisone, and dexamethasone has been used in the past with therapeutic effects in many patients with asthma. However, when used in effective doses, most of these preparations were sufficiently absorbed from the bronchial tree to induce suppression of adrenal function. This is in contrast

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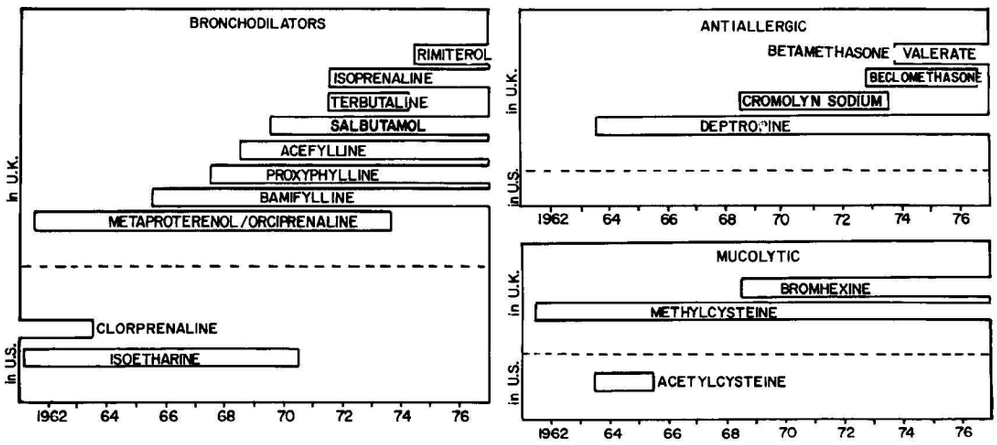


**Fig. 3.** Exclusive availability of respiratory drugs.

**Table V.** *Introduction of respiratory drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | Britain | U.S. | Britain | U.S. |
| *Bronchodilators* | | | | |
| Metaproterenol/orciprenaline (Alupent) | 6/62m | 7/73 | 133 | |
| Terbutaline (Bricanyl) | 6/71 | 3/74 | 33 | |
| Rimiterol (Pulmadil) | 6/74m | — | | |
| *Antiallergics* | | | | |
| Cromolyn sodium (Intal, U.K., U.S.; Aarane, U.S.) | 12/68m | 6/73 | 54 | |
| Beclomethasone dipropionate (Becotide inhaler, U.K.; Vanceril, U.S.) | 11/72m | 5/76 | 42 | |
| Betamethasone valerate† (Bextasol inhaler) | 9/73m | — | | |

*Date of marketing is indicated by "m."

†Not NCE but important new dose form (inhaler). This was not included in the numerical summaries (Tables I and II).

to beclomethasone dipropionate and betamethasone valerate which have been found to be highly effective but to date have not been found to induce appreciable suppression of hypothalamic/pituitary/adrenal function. With the use of these aerosolized steroid preparations in therapeutic doses, most steroid-dependent asthmatics can substantially reduce or eliminate the need for orally administered steroids.

Side effects from these preparations have not been serious, the main one of importance being candida infection of the larynx and pharynx, which appears to be dose-related. To date there have been few reports of serious pulmonary or systemic candida infections. The development of these new aerosolized steroid preparations is a major advance in the treatment of asthma and has already had a significant impact on the therapeutic regimen for this disease.

In summary, after long lag periods, the main gaps in the respiratory field were eliminated by the introduction to the U.S. of bronchoselective bronchodilators, and of cromolyn and beclomethasone. Bromhexine continues to be exclusively available in Britain, showing modest utility as a sputum liquefier in chronic bronchitis.

***Anti-infective drugs.*** Although significant anti-infective drugs were not available in the U.S., these were relatively few. The introduc-

been serious, the main one of importance being candida infection of the larynx and pharynx, which appears to be dose-related. To date there have been few reports of serious pulmonary or systemic candida infections. The develop-

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***Anti-infective drugs.*** Although significant anti-infective drugs were not available in the U.S., these were relatively few. The introduc-

**Table VI.** *Introduction of anti-infective drugs, 1972 to 1976*

| | *Date of introduction** | | *Lead in months* | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *Penicillins* | | | | |
| Amoxicillin (Amoxil) | 2/72 | 1/74 | 23 | |
| Carbenicillin indanyl sodium (Geocillin) | — | 10/72 | | |
| Carfecillin (Uticillin) | 9/74m | — | | |
| Talampicillin (Talpen) | 10/75m | — | | |
| Ticarcillin disodium (Ticar) | — | 11/76 | | |
| *Cephalosporins* | | | | |
| Cephradine (Eskacef, U.K.; Velosef, U.K., U.S.) | 9/72 | 8/74 | 23 | |
| Cephazolin (Kefzol, U.K.; Ancef, U.S.; | 6/74m | 10/73 | | 8 |
| Cephapirin (Cefadyl) | — | 3/74 | | |
| Cephacetrile (Celospor) | — | 9/74 | | |
| *Others* | | | | |
| Co-trimoxazole (Septrin, U.K.; Bactrim, U.K., U.S.; Septra, U.S.) | 10/68m | 7/73 | 57 | |
| Minocycline (Minocin) | 7/72 | 6/71 | | 13 |
| Spectinomycin (Trobicin) | 9/72 | 6/71 | | 15 |
| Oxolinic acid (Prodoxol, U.K.; Utibid, U.S.) | 6/74m | 7/75 | 13 | |
| Tobramycin (Obracin, U.K.; Nebcin, U.S.) | 9/74m | 6/75 | 9 | |
| Sulfacytine (Renoquid) | — | 9/75 | | |
| Amikacin (Amikin) | 12/76m | 7/76 | | 5 |
| *Antifungals* | | | | |
| Clotrimazole (Canesten, U.K.; Lotrimin, U.S.) | 11/72 | 2/75 | 27 | |
| Miconazole nitrate (Daktarin, U.K.; Monistat, U.K., U.S.; Micatin, U.S.) | 6/74m | 1/74 | | 5 |
| *Anthelmintics* | | | | |
| Mebendazole (Vermox) | 9/76m | 6/74 | | 27 |
| *Antivirals* | | | | |
| Idoxuridine (Herpid) | 4/74m | — | | |
| Vidarabine (Vira-A) | — | 11/76 | | |

*Date of marketing is indicated by "m."

tion of co-trimoxazole in the U.S., 5 years after its marketing in Britain, substantially cleared the backlog of useful drugs in this category that were not available in the U.S. Two newer antibiotics, spectinomycin and minocycline, were introduced earlier in the U.S. while others, such as tobramycin and amikacin, were introduced more or less simultaneously in both countries (Table VI and Fig. 4).

In the field of penicillins and cephalosporins, there were some minor advances in which both countries shared equally; at the end of 1976 the U.S. had two cephalosporins not available in Britain. Fusidic acid, which was discussed in the earlier papers, is still not available in the U.S.

In the field of antiparasitic therapy, there are several drugs marketed exclusively in Britain. However, some of these are available in the U.S. through the Center for Disease Control, under INDs that permit therapeutic use.

***Anticancer and immunosuppressive drugs.*** In the earlier report, this was identified as an area in which the U.S. and Britain were approximately comparable with equal numbers of new drugs exclusively available in each country and no prominent clinical discrepancies on either side (Table VII and Fig. 5).

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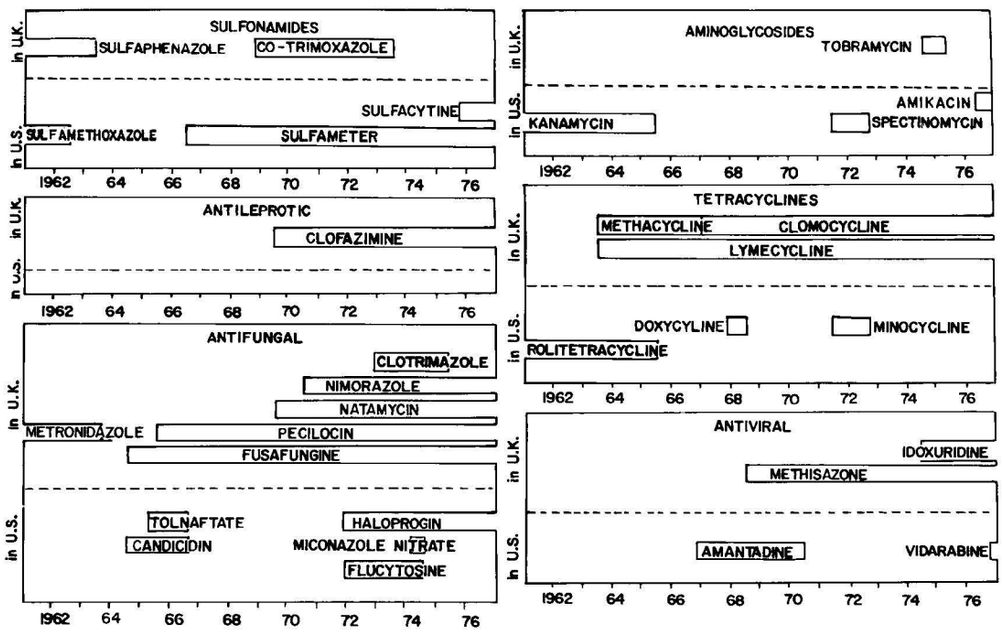


**Fig. 4A.** Exclusive availability of anti-infective drugs.

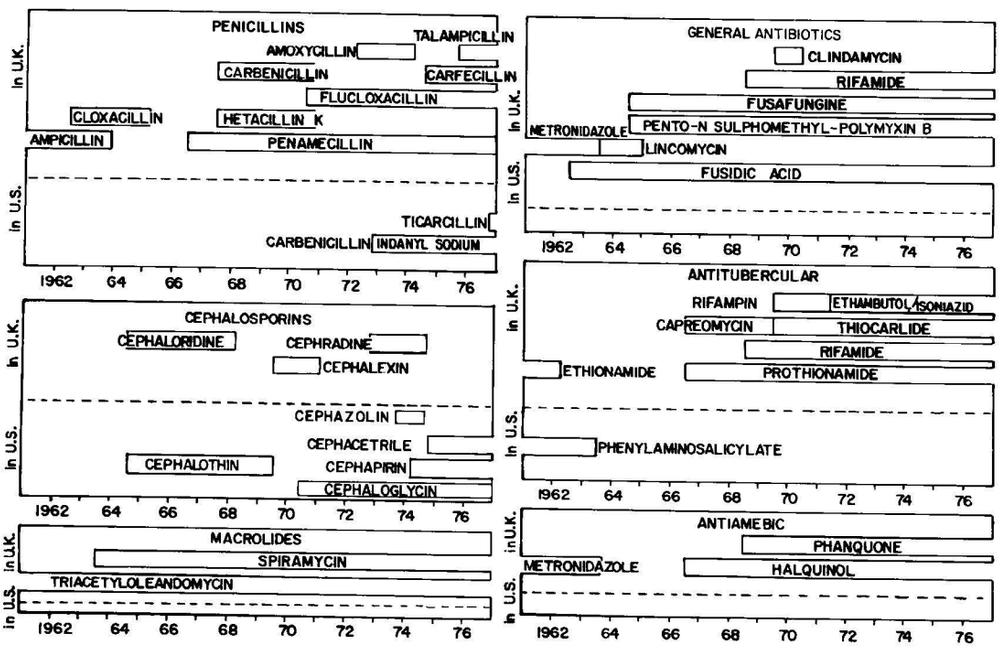


**Fig. 4B.** Exclusive availability of anti-infective drugs.

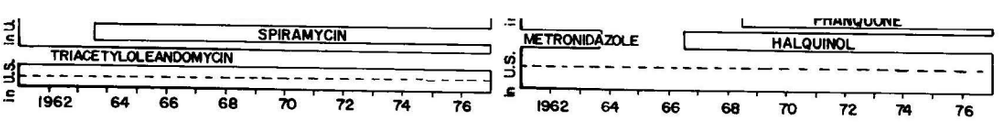


**Fig. 4B.** Exclusive availability of anti-infective drugs.

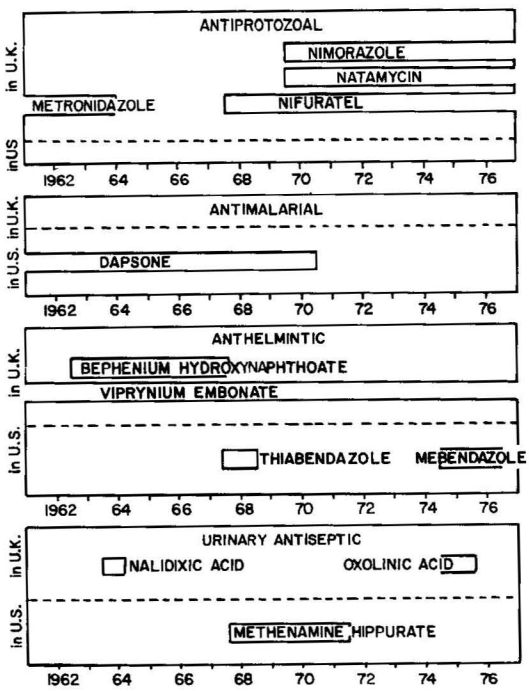


**Fig. 4C.** Exclusive availability of anti-infective drugs.

This pattern was maintained. The therapeutic consequences of the differences that existed in this 5-year period need to be explored in more detail, but do not appear to be major.

***Centrally acting drugs.*** Many more new centrally acting drugs were introduced exclusively into Britain from 1972 through 1976 than into the U.S. The drugs in this area are best considered by therapeutic subcategory (Table VIII and Fig. 6).

*Major tranquilizers.* A larger number of drugs in this category were exclusively available in Britain than in the U.S. The available evidence does not point to any outstandingly good or bad drugs exclusively available in either country.

Flupenthixol, a major tranquilizer, is exclusively available in Britain. It has been shown to be effective in the treatment of schizophrenia and major psychosis. When used in low doses it also induces an antidepressant effect with less evidence of side effects than other widely used antidepressant drugs. Flupenthixol is also available in the long-acting depot injectable form. A somewhat similar drug in depot form, fluphenazine decanoate, is available in the U.S.

Molindone is an indole derivative and represents a new class of psychotropic drug structurally unrelated to the phenothiazines. It is exclusively available in the U.S. Molindone has been reported to possess definite antipsychotic and questionable antidepressant properties. Even though this drug is considered to be a useful alternative to phenothiazines, controlled clinical trials have not yet demonstrated any advantages over available phenothiazines either in terms of efficacy or safety. Molindone has a slow onset of action.

Loxapine is a major tranquilizer that has been exclusively available in the U.S. since 1975. Loxapine, a dibenzoxazepine, is a new chemical entity (NCE) offered as an alternative for the treatment of schizophrenia. As with molindone, clinical studies have not demonstrated any definite superiority over currently used phenothiazines; the side effects have also been similar to phenothiazines. However, the utility of having a wide range of drugs available to enable physicians to tailor drugs to individual patients is a very important consideration in this therapeutic category.

*Minor tranquilizers.* Relatively more minor tranquilizers were available in Britain than in the U.S. The available data do not, however, indicate any noteworthy drugs exclusively available in either country.

*Antidepressants: Non-monoamine oxidase (MAO) antidepressants.* There were 12 non-MAO antidepressants exclusively available in Britain, half of them introduced in 1972 to 1976; there were none exclusively available in the U.S. The major tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, imipramine, desipramine, and doxepin, were introduced at nearly the same time in both countries. The newer drugs available in Britain, such as clomipramine, dibenzepin, butriptyline, and maprotiline, while effective in the treatment of depressive disorders, have not yet been demonstrated to have overall advantages in terms of efficacy over the more familiar earlier TCAs. Some very useful differences in toxicity and side effects have, however, been demonstrated.

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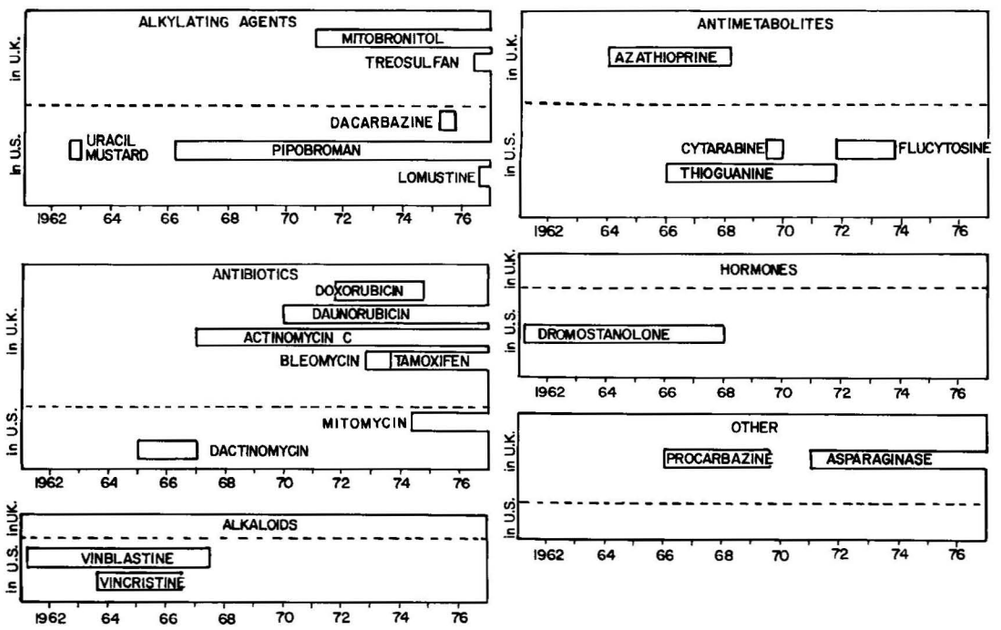


**Fig. 5.** Exclusive availability of anticancer drugs.

**Table VII.** *Introduction of anticancer drugs, 1972 to 1976*

| Drug | *Date of introduction** | | *Lead in months* | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *Anticancer* | | | | |
| Thioguanine (Lanvis, U.K.; Thioguanine Tabloid, U.S.) | 12/71 | 1/66 | | 71 |
| Flucytosine (Ancobon) | 9/73 | 11/71 | | 22 |
| Doxorubicin (Adriamycin) | 11/71m | 8/74 | 33 | |
| Bleomycin (Bleomycin) | 9/72 | 7/73 | 10 | |
| Tamoxifen (Nolvadex) | 7/73 | — | | |
| Mitomycin (Mutamycin) | — | 5/74 | | |
| Dacarbazine (DTIC-Dome) | 10/75m | 5/75 | | 5 |
| Treosulfan (treosulfan) | 5/76m | — | | |
| Lomustine (CeeNU) | — | 8/76 | | |

*Date of marketing is indicated by "m."

Viloxazine has the extremely important attribute of relative safety in acute overdosage. This is a crucial feature of a drug designed for a disease in which attempts at suicidal drug overdose are common and for which the mainstay of drug therapy in the U.S. (the tricyclic family of compounds) is potentially cardiotoxic. Viloxazine has now been available in Britain for 3 years and reports of severe toxicity are rare. Doses of several grams of viloxazine in suicide attempts have been closely followed and little or no cardiac toxicity has been reported. This low toxicity could make viloxazine as important a safety advance as the benzodiazepines were in the field of sedative-hypnotics, since, with the advent of benzodiazepines and the resultant lowering of mortality from the barbiturates they replaced, poisoning by TCAs has become one

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**Table VIII.** *Introduction of centrally acting drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | Britain | U.S. | Britain | U.S. |
| *Major tranquilizers* | | | | |
| Fluphenazine decanoate† (Modecate, U.K.; Prolixin Decanoate, U.S.) | 12/68m | 6/72 | 42 | |
| Flupenthixol (Depixol) | 2/72 | — | | |
| Benperidol (Anquil) | 4/73 | — | | |
| Molindone (Moban) | — | 1/74 | | |
| Loxapine (Loxitane) | — | 2/75 | | |
| Fluspirilene (Redeptin) | 6/75m | — | | |
| *Minor tranquilizers* | | | | |
| Clorazepate (Tranxene) | 2/73 | 6/72 | | 8 |
| Lorazepam (Ativan) | 7/72 | — | | |
| Prazepam (Verstran) | —‡ | 12/76 | | |
| *Antidepressants* | | | | |
| Viloxazine (Vivalan) | 11/74m | — | | |
| Butriptyline (Evadyne) | 2/75m | — | | |
| Maprotiline (Ludiomil) | 3/75m | — | | |
| Mianserin (Bolvidon) | 5/76m | — | | |
| *Hypnotics* | | | | |
| Flurazepam (Dalmane) | 10/73 | 4/70 | | 42 |
| *Antiemetics, Antimigraine* | | | | |
| Clonidine (Dixarit, U.K.; Catapres, U.S.) | 8/71m | —§ | | |
| Benzquinamide (Emete-Con) | — | 3/74 | | |
| Pizotifen (Sanomigran) | 10/75m | — | | |
| *Anticonvulsants* | | | | |
| Clonazepam (Rivotril, U.K.; Clonopin, U.S.) | 8/74m | 6/72 | 10 | |
| Sodium valproate (Epilim) | 11/74m‖ | — | | |
| *Muscle relaxants* | | | | |
| Baclofen (Lioresal) | 6/72 | — | | |
| Dantrolene (Dantrium) | 4/73 | 1/74 | 9 | |
| *Anorectics* | | | | |
| Fenfluramine (Ponderax) | 10/63m | 6/73 | 116 | |
| Mazindol (Teronac, U.K.; Sanorex, U.S.) | 2/73 | 6/73 | 4 | |
| Clortermine (Voranil) | — | 6/73 | | |
| *Antiparkinsonian* | | | | |
| Benapryzine (Brizin) | 7/73 | — | | |
| Levodopa/carbidopa (Sinemet) | 9/73 | 5/75 | 20 | |
| Levodopa/benserazide (Madopar) | 10/74m | — | | |

*Date of marketing is indicated by "m."

†Long-acting dose form. This compound is excluded from the numerical summaries (Tables I and II).

‡Approved in Britain but not yet available.

§Not approved for migraine in the U.S. This drug is included in the numerical summaries in the cardiovascular area.

‖Approved in 1972 for hospital use only.

of the major self-poisoning emergencies in medicine.

Mianserin, an antidepressant recently introduced in Britain but not available in the U.S., represents a new class of drugs. It is a piperazino-azepine compound not structurally related to either tricyclics or MAO inhibitors. Controlled clinical trials have demonstrated mianserin to be as effective as amitriptyline in primary depressive illness, but there was a striking difference in side effects between mianserin and amitriptyline. Mianserin was followed by a

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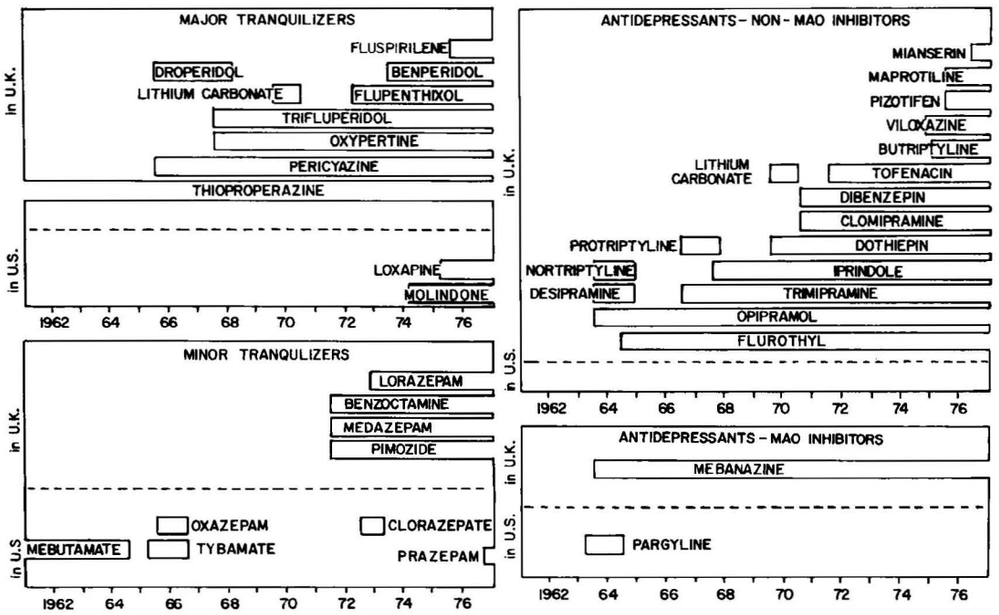


**Fig. 6A.** Exclusive availability of CNS drugs.

lower incidence of total reported side effects, indicating that it not only had relatively fewer significant side effects but that it also improved those symptoms of the illness which resembled or were confused with drug side effects; in this respect mianserin is clearly superior to amitriptyline. Unlike TCAs, mianserin is devoid of side effects due to interaction with adrenergic and cholinergic systems. The mode of action of mianserin is still obscure. Even though at higher doses it inhibits the uptake of serotonin, in doses used to treat depression the drug does not influence the reuptake of amines nor is it an MAO inhibitor. The apparent lack of effect on amines is difficult to reconcile with the biogenic amine theory of affective disorders. It is likely that elucidation of its mode of action will throw fresh light on the chemical pathology of affective disorders.

*Antidepressants. MAO inhibitors.* No new MAO inhibitor was introduced in either country since 1963-1964.

*Antiparkinsonian drugs.* Levodopa, which was introduced in 1971 in both countries for the treatment of parkinsonism, has significantly altered the therapy of this disease.

Concurrent administration of levodopa with a decarboxylase inhibitor allows a greater proportion of the administered levodopa to reach the target receptor sites in the nigrostriatum. Carbidopa is the only approved dopa-decarboxylase inhibitor available in the U.S. It is available as a combination tablet with levodopa in a 1:10 ratio (Sinemet). A 2-year British lead in the approval of carbidopa and also the exclusive availability of another decarboxylase inhibitor (benserazide) in combination with levodopa (Madopar) in Britain are noteworthy. Benserazide in combination with levodopa is as effective as carbidopa with levodopa.

Amantadine was first introduced in the U.S. in 1966 as an antiviral agent against Asian $A_2$ influenza virus. Even though it was available in the U.S. 4 years earlier than in Britain, its use in parkinsonism was approved only in 1973, i.e., 3 years after it became available in Britain for this indication.

*Muscle relaxants: Centrally acting.* Tetrabenazine is exclusively available in Britain. It is a centrally acting drug having certain pharmacologic effects similar to those of reserpine, but its action is more rapid in onset and shorter in duration. It causes depletion of serotonin and

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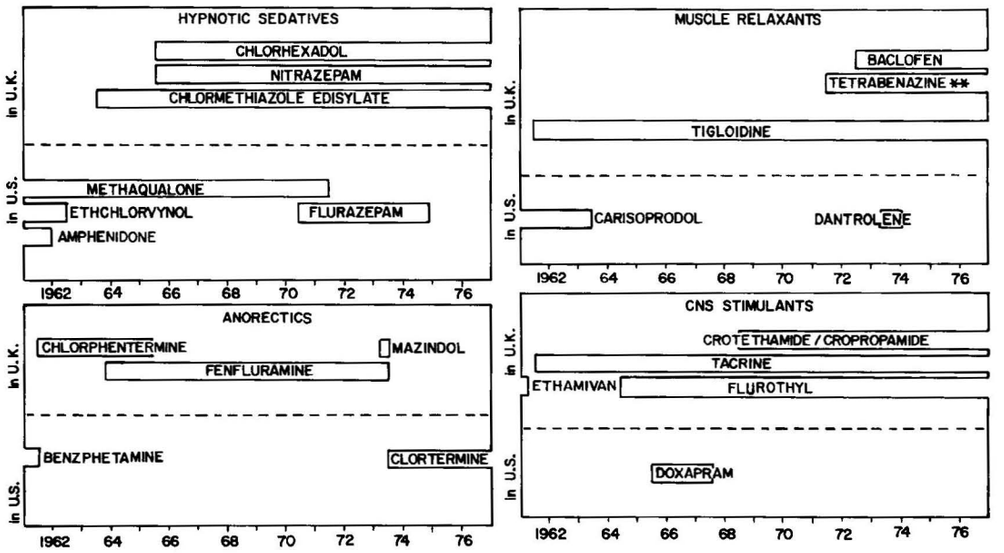


**Fig. 6B.** Exclusive availability of CNS drugs. **This drug was approved earlier for a different indication.

norepinephrine in the brain but, unlike reserpine, it appears to have little effect on the concentration of these monoamines in peripheral tissues. Tetrabenazine has been used in the treatment of dyskinesias and extrapyramidal disorders and there is also some evidence that it can be effective in Huntington's chorea.

Baclofen, a centrally acting derivative of gamma-aminobutyric acid which has muscle relaxant properties, was also exclusively available in Britain through 1976. The relief of symptoms of spasticity by baclofen has been documented in several clinical trials. Baclofen, however, shows differences in therapeutic responses in different types of neurologic lesions, patients with multiple sclerosis and spinal injuries responding better than those with cerebral lesions.

*Muscle relaxants: Direct acting*. Dantrolene represents a new class of drugs that have a direct relaxant action on skeletal muscle. This drug was marketed in the U.S. a year earlier than in Britain. It produces relaxation and reduces contraction of skeletal muscle by a direct action on excitation-contraction coupling, possibly by decreasing the amount of calcium released from the sarcoplasmic reticulum. Dantrolene provides significant and sustained reduction of spasticity and has been shown to improve functional capacity in patients with paraplegia, hemiplegia and multiple sclerosis. Tolerance to its therapeutic effect does not appear to develop, but the drug tends to induce generalized muscle weakness that can be detrimental to functional improvement. There are some recent reports of hepatotoxic reactions. Although the incidence of such a reaction is low (0.1 to 1.8%), it can be serious. Dantrolene may represent a significant advance in the medical management of spastic disorders.

*Anorectics*. A new class of anorectics without amphetamine-like and certain other side effects was brought to the U.S. in 1973 with the introduction of fenfluramine, clortermine, and mazindol. Of these, fenfluramine had been available in Britain for about 10 years.

A 10-year British lead in the approval of fenfluramine is noteworthy. Fenfluramine is a phenylethylamine that lacks certain undesirable features of the amphetamines. In the treatment of obesity fenfluramine has efficacy comparable to that of amphetamines. Although dependence can be demonstrated after chronic use, the drug has less potential for abuse than amphetamines. Fenfluramine has been shown not to antagonize the actions of antihypertensive agents, an im-

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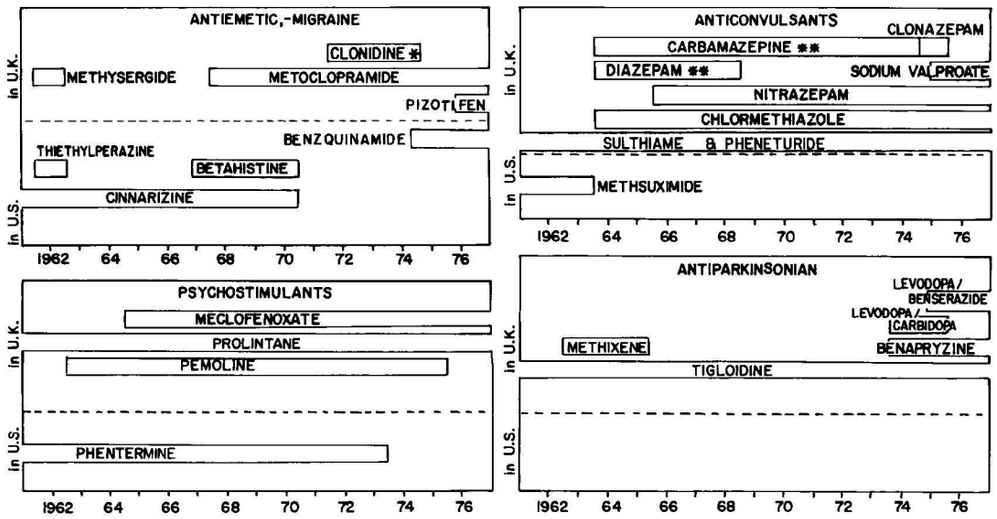


**Fig. 6C.** Exclusive availability of CNS drugs. *This drug has not been approved for migraine in the U.S. **This drug was approved earlier for a different indication.

portant consideration in patients who are both obese and hypertensive.

Clortermine is another phenylethylamine similar to fenfluramine, with similar pharmacologic properties. It is now exclusively available in the U.S.

Mazindol, an imidazolethylamine and therefore the only anorectic that is not a phenylethylamine, is believed to exert its effect in part by facilitating electrical activity in the septal area of the brain. Mazindol was marketed in the U.S. in 1973, a year earlier than in Britain. It has similar anorectic activity without the side effects or, at least as experienced so far, the abuse potential of the amphetamine anorectics.

*Anticonvulsants.* From 1960 through 1976 a total of 11 anticonvulsant drugs were approved for marketing in the U.S. or Britain.[24] Two of these (sodium valproate and clonazepam) appeared after 1972 (valproate being exclusively available and clonazepam mutually available), while the use of one already marketed drug (carbamazepine) was approved for epilepsy in the U.S. some 11 years after its marketing in Britain for this purpose.

Considering all of the 11 drugs, there were substantial differences between Britain and the U.S. in the drugs available for epilepsy by the end of 1976. Five of the drugs were introduced exclusively in Britain, and 6 were introduced in both countries. None was exclusively introduced into the U.S. Of the 6 drugs introduced into both countries, one (methsuximide) was available first in the U.S., but this drug is similar to ethosuximide, which was already available in both countries. The other 5 mutually available drugs all became available (or were approved for epilepsy) earlier in Britain than in the U.S., in some cases by many years. The 5 antiepileptic drugs exclusively available in Britain were pheneturide, sulthiame, chlormethiazole, nitrazepam, and valproate.

Most of the drugs shown here were described in our earlier study. Sulthiame and pheneturide are valuable drugs in some patients, while nitrazepam is still one of the major drugs for childhood seizures.

Of the drugs introduced during the 1972 to 1976 period, sodium valproate is of particular interest. It was introduced in Britain in 1972 and became a treatment of choice for generalized epilepsy, partly because of its effectiveness in some patients in whom standard therapy had failed, and partly because it lacks the marked CNS-depressant side effects of the other antiepileptic drugs. The importance of valproate is exemplified by the fact that the Congressionally-instituted National Commis-

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**Table IX.** *Introduction of anesthetic drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months† | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *General anesthetics* | | | | |
| Alphaxalone/alphadolone (Althesin) | 3/72 | — | | |
| Trifluoroethyl difluoromethyl ether (Ethrane) | — | 8/72 | | |
| *Local anesthetics* | | | | |
| Bupivacaine (Marcain, U.K.; Marcaine, U.S.) | ?/68m | 10/72 | (52) | |
| Etidocaine (Duranest) | — | 8/76 | | |
| *Neuromuscular blocking* | | | | |
| Pancuronium (Pavulon) | ?/68m | 10/72 | (52) | |
| Fazadinium (Fazadon) | 11/76m | — | | |

*Date of marketing is indicated by "m."

†For those British drugs for which the month is not known, calculation of the lead was based on a June date and these values are given in parentheses. These estimates may thus be in error by up to six months in either direction.

sion for the Control of Epilepsy and Its Consequences devoted an entire day's meeting in April, 1977, to a consideration (which involved interrogation of industry and FDA representatives) of why there was at that time still no early prospect for its marketing in the U.S. During the course of these hearings it developed that the drug had been successfully used in Britain and Europe in over 100,000 patients, and its benefit-to-risk ratio was well characterized. Submission of an NDA in the U.S. was awaiting the completion of clinical trials in a few score American patients. The staff of the Commission estimated that the absence of this one drug on the U.S. market was subjecting American patients to approximately 1,000,000 unnecessary seizures a year at a cost of approximately $200,000,000 a year.

Thus from 1960 through 1976 all but one of the 11 drugs introduced for epilepsy in the U.S. or Britain were introduced first in Britain (by margins of up to 11 years, based on date of approval for antiepileptic usage); and half of the drugs were not yet available in the U.S. Those drugs unavailable included important major antiepileptic drugs such as sodium valproate. They also included drugs such as nitrazepam and sulthiame that, while not of great importance to large numbers of epileptics, are known to be uniquely effective in some patients.

*Antimigraine drugs.* From 1971 through 1976 one new drug, pizotifen, became available for prophylactic use in the treatment of migraine in Britain. It was not available in the U.S. While it appears not to be as effective as methysergide, it is safer since it has not been implicated in causing side effects as serious as retroperitoneal fibrosis. There is a significant rate of response to pizotifen, and it can therefore serve as a useful drug with which to initiate prophylactic therapy.

Clonidine is also approved for the treatment of migraine in Britain in a smaller dose form than for hypertension. Clonidine and propranolol are both available in the U.S. but are not approved for migraine, in which they have been shown to be very useful in some patients.

In summary, many more drugs are available in Britain than in the U.S. that act on the central nervous system. In some clinical subcategories, such as the antiepileptics there are clear advantages to patients in Britain for whom there are available newer, more effective, or less toxic drugs. In some areas, such as minor tranquilizers, no clinical significance results from the differences; in other areas, such as antidepressants, new structural classes are available that are of theoretical interest, but whether a major clinical advantage exists in terms of efficacy is not yet known. In terms of safety and side effects, however, there are clear advantages to some of the drugs available abroad but not in the U.S.

***Anesthetic drugs.*** In the area of general an-

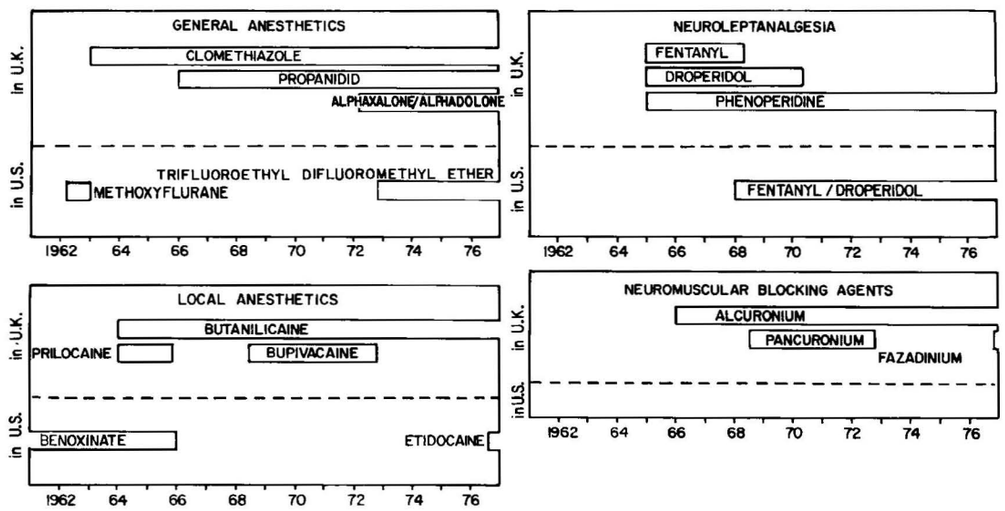


**Fig. 7.** Exclusive availability of anesthetic drugs.

esthetics, the range of drugs available exclusively in Britain was widened by the exclusive introduction there of the short-acting intravenous anesthetic alphaxalone, alphadolone. Conversely, the inhalational anesthetic enflurane was introduced exclusively in the U.S. (Table IX and Fig. 7).

In the area of neuromuscular blocking drugs, pancuronium was introduced to the U.S. after a lag of approximately 4 years; another short-acting competitive drug is now available in Britain.

***Analgesic and related drugs.*** Six new nonsteroidal anti-inflammatory drugs appeared in the 5-year period. This brought the number that appeared since 1962 to 11: 5 of these were available in both countries, 5 were available exclusively in Britain, and one was available exclusively in the U.S. In general, the drugs are fairly similar in efficacy, at least in terms of the ceiling effect if the dose is increased sufficiently. The main advantages that can be claimed for some of the newer members are different pharmacokinetics (e.g., allowing less frequent and therefore more convenient dosing schedules) and a diminished incidence—or at least a different spectrum—of side effects compared with the older alternatives such as aspirin or phenylbutazone. With some of these newer drugs an improved therapeutic ratio has indeed been claimed, but the type of proof available is in most cases not yet rigorous and there are relatively few comparisons of the various drugs in specific subpopulations of patients. In my opinion, the range of drugs now available (and the expanded range that is on the horizon) would be better justified if subgroups of patients were identified in whom specific advantages for one or another drug could be shown. In view of the known needs of different patients for different drugs, and of the clinical experience with existing compounds to date, this should not be too difficult but it has not yet been done for most of these drugs (Table X and Fig. 8).

In the case of narcotics and narcotic antagonists, there was a British lag in the introduction of the pure narcotic antagonist, naloxone over 2 years after its introduction in the U.S.

***Gastrointestinal drugs.*** This is an area in which, as shown in our original papers, there were several interesting drugs available in Britain but not in the U.S. In the field of peptic ulcer by the end of 1976 the U.S. lacked the only two drugs that have been unequivocally shown to exert a healing effect on peptic ulcer: carbenoxolone (introduced in Britain in 1963) and cimetidine (the first $H_2$ antagonist; introduced there in 1976) (Table XI and Fig. 9).

Gastrointestinal drugs that had previously been available exclusively in Britain, such as

schedules) and a diminished incidence—or at least a different spectrum—of side effects compared with the older alternatives such as aspirin or phenylbutazone. With some of these newer drugs an improved therapeutic ratio has indeed

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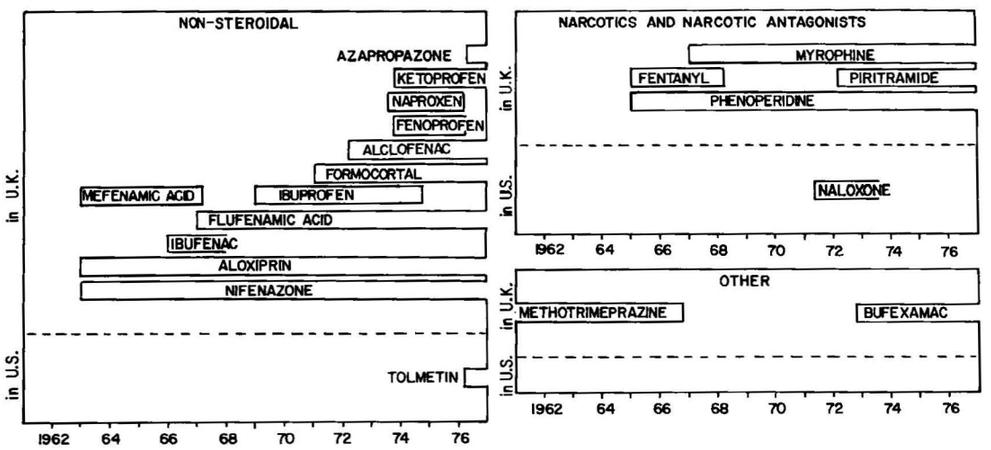


**Fig. 8.** Exclusive availability of analgesic and anti-inflammatory drugs.

**Table X.** *Introduction of analgesic and related drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *Nonsteroidal analgesics and anti-inflammatories* | | | | |
| Ibuprofen (Brufen, U.K.; Motrin, U.S.) | 2/69m | 9/74 | 67 | |
| Alclofenac (Prinalgin) | 3/72m | — | | |
| Naproxen (Naprosyn) | 7/73 | 3/76 | 32 | |
| Ketoprofen (Orudis) | 9/73 | — | | |
| Fenoprofen (Fenopron, U.K.; Nalfon, U.S.) | 10/73 | 3/76 | 29 | |
| Tolmetin (Tolectin) | — | 3/76 | | |
| Azapropazone (Rheumox) | 4/76m | — | | |
| *Narcotic type and narcotic antagonists* | | | | |
| Naloxone (Narcan) | 7/73 | 4/71 | | 27 |
| Piritramide (Dipidolor) | 2/72m | — | | |
| *Others* | | | | |
| Bufexamac (Feximac), topical | 12/72 | — | | |

*Date of marketing is indicated by "m."

lactulose and pentagastrin, were introduced into the U.S. after lags of more than 6 years. In other respects the status of this area was unchanged, with several other interesting but probably not vital drugs continuing to be available abroad.

## Discussion and conclusions

In the previous study covering the decade through 1971, we found large differences of clinical importance between the U.S. and Britain in the therapeutic fields represented by cardiovascular, diuretic, respiratory, anti-infective, and gastrointestinal drugs. This study shows that in the subsequent 5 years, the relationship changed perceptibly—not so much in the relative numbers of new drugs that became available (in which Britain still substantially exceeded the U.S.), but in the narrowing of the most obvious therapeutic differences between the two countries.

In the anti-infective area, by the end of 1976 there was little difference between the two countries; in fact, some useful new antibiotics

## Discussion and conclusions

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In the anti-infective area, by the end of 1976 there was little difference between the two countries; in fact, some useful new antibiotics

**Table XI.** *Introduction of gastrointestinal drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months† | |
|---|---|---|---|---|
| | Britain | U.S. | Britain | U.S. |
| *Peptic ulcer* | | | | |
| Cimetidine (Tagamet) | 11/76 | — | | |
| *General* | | | | |
| Lactulose (Duphalac, U.K.; Cephulac Syrup, U.S.) | 3/69m | 3/76‡ | 84 | |
| Hydrotalcite (Altacite) | 11/72 | — | | |
| Loperamide (Imodium) | 5/75m | 12/76 | 19 | |
| *Diagnostics* | | | | |
| Pentagastrin (Peptavlon) | ?/67m | 7/74 | (85) | |

*Date of marketing is indicated by "m."

†For those British drugs for which the month is not known, calculation of the lead was based on a June date and these values are given in the parentheses. These estimates may thus be in error by up to six months in either direction.

‡Approved only for portocaval encephalopathy in U.S.

were approved earlier in the U.S. than in Britain. In the respiratory field, after substantial delays the most important differences were essentially eliminated. The remaining fields in which the U.S. was still behind Britain with respect to therapeutically important drugs by December, 1976, included the cardiovascular area, peptic ulcer, and epilepsy*; some of the discrepancies in these areas had been present for over 10 years. In other areas only scattered differences were observed which, while mostly in the direction of a British lead, did not form as strong and consistent patterns as before. It should be noted, however, that the present clinical interpretations of the differences between the countries deal only with the most obvious differences, and further examination of more subtle properties of the drugs presently not available in the U.S. would be likely to increase the interpreted clinical significance of these differences.

The reasons for the narrowing of the large differences between Britain and the U.S. are many and the relative importance of each cannot be completely determined. It should be clearly understood that the patterns we have described here are the result of both regulatory and industrial policies and actions (or lack of them) and that the existence of a lag does not imply one cause over another. Although there are cases of a clear delay because of a firm's failure to file an Investigational New Drug (IND) or New Drug Application (NDA), as well as other cases where there has obviously been excessive regulatory inhibition, many more cases involve a complex mixture of the two causes which cannot be resolved without complete knowledge of the facts and assessment of the opposing arguments. Thus, does a delay in filing (or failure to file) an NDA mean that a firm is slothfully heedless of future profits or that it is diligently accumulating what it perceives to be enough data to satisfy FDA's high standards? Such determinations were beyond the scope of this study.

Among the regulatory factors contributing to the convergence in patterns of drug availability are changes in policies in both the U.S. and Britain. In certain respects by 1976 U.S. drug regulatory policies had become more consistent with current world standards of professional and scientific thought. In the early 1970s, FDA management made an effort to remedy what it perceived to be barriers in the regulatory process,[11] and the changes that were implemented improved the FDA's standing in the scientific and medical communities. The increased supervision and guidelines relating to the nature of evidence required for approval have also made NDA approval more predictable. In Britain,

*During 1977 and early 1978, changes were occurring in the U.S. which would appear to narrow disparities still further. However, since full details of the comparable changes in Britain for the same period were not available, we consider here the 5-year period through December 31, 1976, for which complete data for both countries are available.

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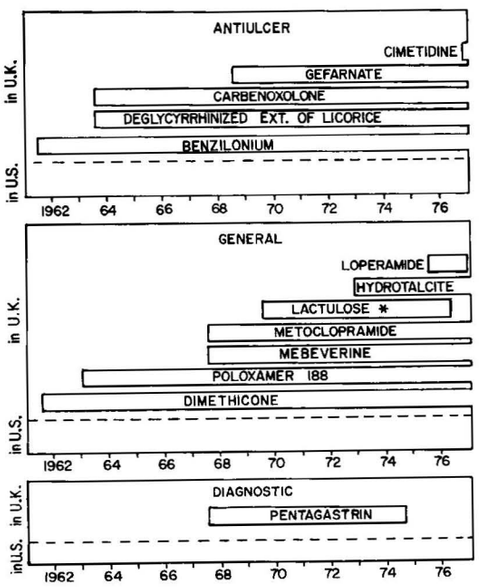


**Fig. 9.** Exclusive availability of gastrointestinal drugs. *This drug has been approved only for portocaval encephalopathy in the U.S.

regulatory requirements have increased rapidly in recent years and a more conservative trend is developing. This change may also have contributed to the convergence.

Another contributing factor may be that our initial studies, together with related studies and increased public awareness of this issue, have had an impact on the phenomenon being investigated. The demonstration of anachronisms in the drug approval process appears to accelerate their correction, as evidenced for example by FDA's handling of the propranolol NDAs for angina and hypertension and of beclomethasone for asthma. FDA's 1975 regulations regarding the acceptance of foreign clinical data and the new administrative procedures for prioritizing IND and NDA submissions according to their importance and degree of attention they are receiving from outside all suggest an awareness at FDA of the public interest in the drug approval process and the problem of drug lag.

The complexity of the risk-benefit decisions that must be made by a regulatory agency and the several types of influences that affect these decisions are well illustrated by the case of the β-blockers. It has been argued (see e.g., Reference 13) that the conservative attitude which FDA adopted toward β-blockers from the mid-1960s to date[6] was beneficial because it delayed by several years (and ultimately prevented) the marketing of practolol, along with several other post-propranolol β-blockers, preventing thereby cases of oculocutaneous and peritoneal toxicity[8] in the U.S. It should be noted, however, that the benefits of practolol to patients following an anterior myocardial infarction greatly outweigh the risks and that the proper use of practolol in postinfarction patients could save at least 10,000 lives per year in the U.S.[26]

Further implications of the delays in introduction of β-blockers to the U.S., including a 7-year setback in cardiovascular therapeutic research in the U.S., have recently been discussed in detail by Wardell.[21] The reasons for conservatism on the β-blockers in the U.S. are complex, as evidenced by the debate on this issue between FDA[4] and one of the industrial sponsors.[3] Substantial reaction against even the belated approval of propranolol for angina came from Congress (by which FDA was unfairly criticized for alleged hastiness in its approval[7, 14, 20]). The tortuous regulatory and scientific milieu that has surrounded the β-blockers in the U.S. is well illustrated in FDA's report on the subject.[6]

Other types of governmental and industrial considerations also influence the patterns of drug availability. In areas such as cancer chemotherapy and narcotic and narcotic-antagonist drug research, in which U.S. government agencies have positive mandates and funding to seek out improved therapies, the U.S. leads other countries in the range of drugs discovered and available. On the industrial side, foreign companies may be becoming more sophisticated in their penetration of the U.S. market (by licensing or by forming subsidiaries) and in satisfying U.S. regulatory standards, thereby contributing to the convergence of therapeutic patterns.

An important point to recognize in interpreting a comparison such as this study is that, since drug innovation and regulation are dynamic processes, a "snapshot" of the situation at one moment in time is less useful than a consideration that takes into account the longer evolu-

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tionary trends. While with some exceptions this study shows a narrowing of the therapeutic differences between the two countries, it also confirms that there have been large differences in the past, and it identifies the patterns and therapeutic areas on which attention should be focused in the future.

Differences in drug approval for specific *indications* are becoming increasingly important in comparative studies of this type. This is because, as stronger controls over drug utilization continue to gain in significance as determinants of therapeutic practice,[23] approval of specific indications becomes nearly as important as the fact of introduction. In Britain, except for those over promotion and excessive drug use, there are few controls; some drugs are approved first for use in hospitals only, which in practice restricts their use to specialists. In the U.S., control over utilization is becoming an important consideration as FDA seeks to increase the detail in the drug label and to constrain use to labeled indications and as the malpractice constraints of using a drug outside its labeling come to be more feared by physicians. Congress is seeking, as evidenced by the bills that have been introduced in the past few years culminating in the Drug Regulation Reform Act of 1978, to give FDA the power to constrain by legal means the power of physicians to prescribe drugs for purposes outside approved labeling. Where possible in our study, data were provided on important differences between approved indications for a drug in addition to information on its initial approval or introduction.

The ease with which gross disparities can be detected between countries suggests that much useful information could be gained by the continuous monitoring of international therapeutic differences. This would not be a difficult task, but it has received very little attention to date, even with respect to English-speaking countries alone. An example of the effect that differences in approval have on drug utilization in different countries is shown for antihypertensive drug usage in the paper by Petursson, Wardell, and Curran.[16] In future studies of this type, therefore, more information will be needed on the exact indications for which mutually available drugs have been approved.

International comparisons such as this should be only the beginning of attempts to chart therapeutic progress and to measure the impact of drugs and their regulation in therapeutic terms. We also need to know how to measure therapeutic impact, beneficial and adverse, that a new drug has on the whole community and—obviously further in the future—how to develop methods to assess the potential therapeutic impact of drugs that are prospective candidates for approval.

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# THE DRUG LAG REVISITED: COMPARISON BY THERAPEUTIC AREA OF PATTERNS OF DRUGS MARKETED IN THE UNITED STATES AND GREAT BRITAIN FROM 1972 THROUGH 1976

WILLIAM M. WARDELL, M.D., PH.D.
Rochester, N. Y.

Center for the Study of Drug Development, Departments of Pharmacology and Toxicology and of Medicine, University of Rochester Medical Center

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## Original articles

# The drug lag revisited: Comparison by therapeutic area of patterns of drugs marketed in the United States and Great Britain from 1972 through 1976*†

*This study describes rates and patterns of new drug introductions in the U.S. and Britain from January, 1972, through December, 1976, updating an earlier study that described the patterns over the previous decade. This comparative international approach enables overall effects of different regulatory, industrial, and other types of changes in drug research and development in the two countries to be evaluated. Numerical differences persisted. In the 1972 to 1976 period, 82 new drugs appeared for the first time in either country. Only 29% of these became mutually available in both countries, 2.4 times as many becoming available first in Britain as in the U.S. Of the 71% that became exclusively available, 2.6 times as many became available in Britain as in the U.S. More important than numerical data are clinical implications of differences between the countries. The largest differences have narrowed since the previous study, but important categories in which the U.S. still lagged behind Britain in December, 1976, included cardiovascular drugs, peptic ulcer drugs, and central nervous system drugs–including therapies for depression, epilepsy, and migraine. Several factors contributed to the narrowing of U.S.–British therapeutic differences, including more realistic regulatory practices and higher quality clinical studies in the U.S., more conservative practices in Britain, attention drawn by previous studies to anachronisms in the U.S., and industrial changes such as more efficient penetration of the U.S. market by foreign firms. It is difficult to determine the relative contribution of each of these factors to the narrowing of the international difference.*

**William M. Wardell, M.D., Ph.D.** *Rochester, N. Y.*
*Center for the Study of Drug Development, Departments of Pharmacology and Toxicology and of Medicine, University of Rochester Medical Center*

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Reprint requests to: William M. Wardell, M.D., Ph.D., Department of Pharmacology, University of Rochester Medical Center, 601 Elmwood Ave., Rochester, NY 14642.

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†A preliminary study of the changes from 1972 through mid-1974 is contained in Wardell, W. M.: Developments since 1971 in the patterns of introduction of new therapeutic drugs in the United States and Britain, *in* Helms, R. B., editor: Drug development and marketing, Washington, D. C., American Enterprise Institute for Public Policy Research, 1975, pp. 165-181.

As a measure of pharmaceutical innovation, information on new chemical entities (NCEs) that reach the point of marketing represents the ultimate expression of the several major influences (notably industrial and regulatory factors) that are involved in the process of drug development.

In 1972, we examined the pattern of introduction of new therapeutic drugs in the United States over the decade that had elapsed since the passage of the Kefauver-Harris drug amendments, and compared this pattern with the cor-

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**Table I.** *Summary of new drug introductions in Great Britain and the United States from January, 1972, through December, 1976**

| | | | *Mutual* | | | | |
|---|---|---|---|---|---|---|---|
| | | | *Britain first* | | *U.S. first* | | *Total mutual drugs* |
| | | *Total* | *Drugs* | *Months†* | *Drugs* | *Months†* | |
| Cardiovascular | (15) | 16 | 2 | 14 | 1 | 27 | 3 |
| Diuretic | (10) | 2 | 1 | 18 | — | — | 1 |
| Respiratory | (8) | 2 | 1 | 42 | — | — | 1 |
| Anti-infective | (47) | 18 | 5 | 19 | 4 | 11.3 | 9 |
| Anticancer | (17) | 6 | 1 | 10 | 1 | 5 | 2 |
| CNS | (36) | 23 | 4 | 10.8 | 1 | 8 | 5 |
| Anesthetic | (10) | 4 | — | — | — | — | — |
| Analgesic | (8) | 8 | 2 | 30.5 | — | — | 2 |
| Gastrointestinal | (7) | 3 | 1 | 19 | — | — | 1 |
| Total | (158) | 82 | 17 | 316 | 7 | 85 | 24 |
| Average | | | | 18.6 | | 12.2 | |
| | | | (32) | | (19) | | (65)‡ |

*Drugs available in either country before 1972 are excluded. The corresponding values for the previous decade are shown in parentheses.
†The mean is given where more than one drug is involved.
‡Fourteen new drugs were introduced in both countries during the same year and were considered to be simultaneous in the previous analysis.

**Table II.** *Summary of new drug introductions in either Britain or the United States from January, 1972, through December, 1976**

| | | *Mutual* | | | | |
|---|---|---|---|---|---|---|
| | | *Britain first* | | *U.S. first* | | *Total mutual drugs* |
| | *Total†* | *Drugs* | *Months‡* | *Drugs* | *Months‡* | |
| Cardiovascular | 17 | 3 | 23.3 | 1 | 27 | 4 |
| Diuretic | 2 | 1 | 18 | — | — | 1 |
| Respiratory | 5 | 4 | 65.5 | — | — | 4 |
| Anti-infective | 21 | 6 | 25.3 | 6 | 12.2 | 12 |
| Anticancer | 9 | 2 | 21.5 | 3 | 32.7 | 5 |
| CNS | 25 | 5 | 31.8 | 2 | 25 | 7 |
| Anesthetic | 6 | 2 | 52 | — | — | 2 |
| Analgesic | 10 | 3 | 42.7 | 1 | 27 | 4 |
| Gastrointestinal | 5 | 3 | 62.7 | — | — | 3 |
| Total | 100 | 29 | 112.4 | 13 | 275 | 42 |
| Average | | | 38.8 | | 21.2 | |

*Drugs previously available in other country before 1972 are included.
†The total includes the exclusively available drugs listed in Table I.
‡The mean is given where more than one drug is involved.

responding pattern in Britain for the same period.[25, 27] In that study, a considerable difference was found in the number and patterns of NCEs marketed in the U.S. and Britain, and clear-cut therapeutic implications of these differences were apparent. British usage and American awareness of some new therapeutic drugs were surveyed in five therapeutic areas[22] and the implications of the observed substantial international differences in the availability, use, and knowledge of new therapies were analyzed to determine whether, in therapeutic terms, the U.S. had gained or lost from adopting its more stringent regulatory policies. On balance, our conclusion was that Britain appeared to have gained in comparison with the U.S. from its less

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| *Exclusive* | | | | *Total exclusive drugs* |
|---|---|---|---|---|
| *Britain* | | *U.S.* | | |
| *Drugs* | *Months†* | *Drugs* | *Months†* | |
| 13 | 24.1 | — | — | 13 |
| 1 | 42 | — | — | 1 |
| 1 | 30 | — | — | 1 |
| 3 | 24.3 | 6 | 21.2 | 9 |
| 2 | 24 | 2 | 17.5 | 4 |
| 13 | 31.4 | 5 | 26.4 | 18 |
| 2 | 29 | 2 | 28 | 4 |
| 5 | 42 | 1 | 9 | 6 |
| 2 | 25 | — | — | 2 |
| 42 | 123.2 | 16 | 359 | 58 |
| | 29.3 | | 22.4 | |
| (72) | | (21) | | (93) |

restrictive policy toward the marketing of new drugs, coupled with its more developed program of postmarketing surveillance.[28]

This present study extends the same U.S.–British comparison from the beginning of 1972 through the end of 1976 to determine whether any changes have occurred in these 5 years in the pattern of new drug introductions in each country, or in the relationship between them. Identifiable changes in the relationship between the two countries would be of interest, because regulatory approaches in the U.S. and Britain evolved considerably during this period.

In Britain, the Medicines Act (1968) became law in September, 1971. As a result, the review process for new drugs has become more institutionalized, in some respects coming to resemble that of the U.S. In certain respects regulatory control of clinical drug research in Britain has been increasing faster than in the U.S., beginning before the Medicines Act was implemented. The regulatory situation has also become more complex in the U.S. since the early 1970s. In addition to specific and proposed new regulations, several external factors have affected the actions of the FDA's Bureau of Drugs in its review and approval of new drugs. These were well described in the reports of the HEW Review Panel on New Drug Regulation.[10] Thus, in view of the complexity of the influences known to be affecting the process of drug development and approval, the international comparison of drugs reaching the market offers a relatively straightforward way of examining the overall effects of all such factors.

## Methods

The methods used were similar to those in the previous study.[25, 27] As before, the study examines nine major therapeutic areas and deals primarily with new chemical entities, which we define as new molecular structures excluding new salts, esters, dose forms, vaccines, and biologicals. Significant new drugs that fell outside these criteria are referred to in the text or tables but are excluded from the numerical summaries. Thus, although the approval of an existing drug for a new indication may be as important as the availability of a new molecule, new indications are excluded from the numerical summaries (Tables I and II) but are included in the tables and figures for specific therapeutic areas. Each drug is counted only once in the numerical summaries.

The available data sources for Britain primarily cover drugs introduced into general practice; thus, the data will understate the priority of marketing in Britain for those drugs that were introduced earlier in hospitals than in general practice, and may omit certain drugs introduced only into hospitals in Britain. Hence, in the present circumstances, the comparison tends to understate the differences between Britain and the U.S.

Wherever possible, the dates shown are the dates of initial regulatory approval or, where indicated, the date of approval for a specified indication. Such approval dates are available for most U.S. drugs from the FDA, but comparable approval dates are considered confidential by the British government until the drug is marketed. (Most of the approval dates available for Britain were obtained from the Committee on Safety of Medicines.) When publicly available, information was obtained directly from the pharmaceutical company involved. Where subsequent approval dates for different indications are important, these are provided in the tables or text. Where an approval date was not available, the date of marketing was used (obtained from deHaen[5] or MIMS[15] or the firm involved) and a

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mid-year date was assumed for the calculations. Thus, the data actually available are usually the date of approval of a drug for marketing in the U.S. and the date of its marketing in Britain. Again this tends to underestimate the difference between Britain and the U.S., so that the overall comparison presented in this study is conservative in that sense.

## Results

The full results are presented in the form of tables, while graphs are used to show when, and for how long, drugs were exclusively available in each country. For every therapeutic category or subcategory, time is represented horizontally in the graphs and a horizontal dashed line bisects the field. Those drugs that were exclusively available in Britain (or, where the information is accurately known, exclusively approved for a particular use there) are shown above this line, and those in the U.S. below the line. The bar representing each drug extends from the time the drug became exclusively available (or its use exclusively approved) until its exclusive availability ceased—usually because the drug was marketed in the other country but occasionally (where noted) because it was withdrawn or restricted.

Thus, a preponderance of bars above the horizontal line indicates a British lead in exclusively available or usable drugs, while a preponderance below the line indicates an American lead. The length of the bar shows how long the disparity persisted. What is important is not only the number of drugs available, but also their identity and pharmacologic and therapeutic significance. The graphic display is the most useful way to organize this information; a vertical line on the graph at any point on the time axis allows one to examine the differences between the range of drugs exclusively available in each country up to and including that time.

***Numerical summary of new drug approvals from January, 1972, through December, 1976.*** The summary data for this 5-year period are shown in Tables I and II. Table I includes the 82 new drugs that appeared for the first time, while Table II includes an additional 18 "catch-up" drugs that had been exclusively available in one of the two countries prior to 1972 and that became available in the other country during the period 1972-1976.

It is instructive first to compare the rate of appearance of new drugs over the recent 5-year period with the corresponding rate of the previous decade. This comparison is best made on the basis of new drugs that appeared for the first time in the period under consideration. For this purpose, Table I of this paper is compared with Table I of Reference 25, with the "catch-up" entries excluded from the latter. (These exclusions reduced the number of drugs in the 1962 to 1971 table from 180 to 158.) The distribution of the 158 drugs for 1962 to 1971 are shown in brackets in Table I of this paper.

The rate of appearance of new drugs has been approximately the same over these 5 years as the previous decade: a total of 82 new drugs appeared in the 5 years (compared with 158 in the previous 10 years); 24 became mutually available (compared with 65), while 58 became exclusively available (compared with 93).

The large numerical differences in patterns between Britain and the U.S. continued or tended to increase. Considering first only those drugs that appeared after 1971 (Table I), only 29% of the drugs became mutually available in both countries (compared with 41%), of which 2.4 times as many became available first in Britain than became available first in the U.S. (compared with 1.7 times as many). Seventy-one percent of the drugs became exclusively available in one of the two countries (compared with 59%). Of these, 2.6 times as many became exclusively available in Britain as in the U.S. (compared with 3.4 times as many).

Alternatively, 42 drugs that had been available in either country during the 1972 to 1976 period or prior to 1972 were introduced into the other country between 1972 and 1976 (Table II). Of these drugs, 29 were introduced first in Britain, and 13 were introduced first in the U.S. The average lead time for drugs appearing first in Britain was 38.1 months (range, 4 to 133 months), while the average lead time for those appearing first in the U.S. was 24.8 months (range, 5 to 71 months). Expressed as a single index, among those drugs that became mutually available there were 23 "drug years" of prior availability in the U.S., while the correspond-

1976. The summary data for this 5-year period are shown in Tables I and II. Table I includes the 82 new drugs that appeared for the first time, while Table II includes an additional 18 "catch-up" drugs that had been exclusively available in one of the two countries prior to months), while the average lead time for those appearing first in the U.S. was 24.8 months (range, 5 to 71 months). Expressed as a single index, among those drugs that became mutually available there were 23 "drug years" of prior availability in the U.S., while the correspond-

**Table III.** *Introduction of cardiovascular drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *Antihypertensives* | | | | |
| β-Blockers †‡ | 2/69 | 5/76 | 85 | |
| Clonidine (Catapres) | 3/71m | 9/74 | 42 | |
| Diazoxide (Eudemine, U.K.; Hyperstat, U.S.) | ?/72m§ | 1/73 | (7) | |
| Prazosin (Sinetens, Hypovase, U.K.; Minipres, U.S.) | 9/74m | 6/76 | 21 | |
| *β-Adrenoreceptor antagonists* | | | | |
| Sotalol (Beta-Cardone, Sotacor) | 6/74m | — | | |
| Timolol (Blocadren) | 6/74m | — | | |
| Pindolol (Visken) | 10/74m | — | | |
| Acebutolol (Sectral) | 4/75m | — | | |
| Metoprolol (Betaloc, Lopresor) | 7/75m | — | | |
| Atenolol (Tenormin) | 7/76m | — | | |
| *Antiarrhythmics* | | | | |
| Disopyramide (Rythmodan) | 6/72 | — | | |
| Phenytoin (Epanutin)† | 8/73m | — | | |
| Mexiletine (Mexitil) | 4/76m | — | | |
| *Others* | | | | |
| Naftidrofuryl (Praxilene) | 1/72 | — | | |
| Dopamine (Intropin) | 5/76m | 2/74 | | 27 |
| Oxypentifylline (Trental) | 10/75m | — | | |
| Perhexiline (Pexid) | 1/76m | — | | |
| Medigoxin (Lanitop) | 4/76m | — | | |
| *Hypolipidemics* | | | | |
| Polidexide (Secholex) | 5/74m | — | | |

*Date of marketing is indicated by "m."

†Listed here but does not satisfy all criteria for inclusion in numerical summaries (Tables I and II).

‡All β-blockers are approved in Britain for use as antihypertensives. The date of first specific approval for this indication in Britain was for propranolol in February, 1969. It was first approved in Britain in 1965. The first U.S. approval for an antihypertensive action of a β-blocker was for propranolol in May, 1976. It was first approved in the U.S. in November, 1967.

§In the case of hospital use, diazoxide was available earlier than this in Britain. The month of marketing was unavailable so the calculation of the lead was based on a June date.

ing figure for Britain (94 drug years) was 4.1 times as many (Table II).

***Cardiovascular drugs.*** In the original study,[25, 27] the cardiovascular area was identified as one in which particularly large differences had arisen between Britain and the U.S. These numerical differences persisted, as seen from Table I where 13 of the 16 new drugs to appear in this category were introduced exclusively in Britain.

*Antihypertensives.* As seen in Table III and Fig. 1, no antihypertensive drugs were approved in the U.S. for the entire decade, i.e., from the introduction of pargyline and methyldopa in 1963 to the introduction of diazoxide in 1973; by contrast, new antihypertensive drugs continued to appear in Britain. Large differences between the two countries arose in all the major classes of antihypertensive drugs except diuretics. Several β-blockers were well established as major antihypertensive drugs in Britain, propranolol having been approved for this purpose in 1969, whereas the only member of this class available in the U.S. (propranolol) was not approved as an antihypertensive until 1976. Adrenergic-neurone–blocking drugs were used much more extensively abroad than in the U.S., due at least in part to the availability of more convenient members of this class abroad,[16] and other drugs, such as clonidine and

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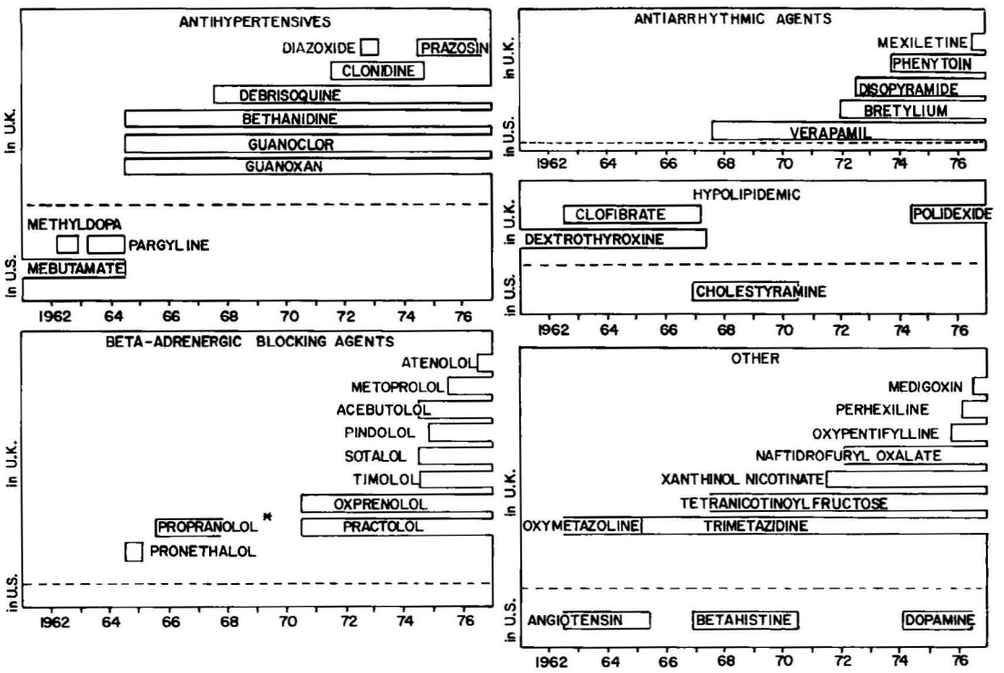


**Fig. 1.** Exclusive availability of cardiovascular drugs. *This drug was available only for restricted indications in the U.S. See text for details.

diazoxide, were valuable alternatives to existing therapy.

In a recent study[16] we explored some of the differences in usage that arose between the U.S. and three other countries (Britain, Australia, and New Zealand) as a result of differences in patterns of availability. We used the national consumption statistics from each country to compute the number of defined daily doses per thousand of population per year (DDD/1,000) for each drug. These values were used to compare per capita consumption of antihypertensive drugs in the four countries. One of the striking differences in usage patterns was the heavy reliance in the U.S. on the older drugs such as rauwolfia alkaloids. On a per capita basis, the consumption of rauwolfia alkaloids in the U.S. by 1972 was more than four times the rate in Britain, and even double the rate in Australia, despite the fact that the total rate of usage of nondiuretic antihypertensives (NDAH) in Australia was considerably higher than in the U.S. On a percentage basis, rauwolfia alkaloids accounted for 75% of the total U.S. NDAH use, while in Britain the fraction was 23%, i.e., less than a third of the U.S. fraction.

Conversely, the use of adrenergic-neurone–blocking drugs was much higher in the other countries than in the U.S. On a per capita basis, the use of these drugs was nearly four times as great in Britain as in the U.S., and more than 10 times as great in New Zealand as in the U.S.; in the latter comparison, the corresponding fractions of the total NDAH use contributed by adrenergic-neurone–blocking drugs were 38% and 5% respectively, representing nearly an eight-fold difference.

Even within the class of adrenergic-neurone–blocking drugs, some interesting differences appeared between the countries as a result of the differences in drugs available. In the U.S., the only member of this class of drugs is guanethidine, while in the other three countries two additional drugs were available, bethanidine and debrisoquin which together accounted for approximately one third of the total adrenergic-neurone blocker usage in these three countries. Thus, comparing New Zealand with

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the U.S. on a DDD/1,000 basis, New Zealand had more than six times the guanethidine consumption, plus an additional consumption (equivalent to nearly four times the U.S. guanethidine consumption) of adrenergic-neurone–blocking drugs that were not available in the U.S.

The per capita use of methyldopa also showed wide international differences, being lowest in the U.S. and highest (by a factor of 3.4 times) in Australia. In terms of the percentage of methyldopa in relation to total NDAH consumption, the U.S. had the lowest ratio (16%), while Britain had the highest (nearly 50%).

A further large difference could be seen in the use of fixed-combination drugs, namely, NDAH in fixed combinations with (for the most part) diuretics. In the case of rauwolfia alkaloids, for example, there were very wide variations in combination use, with the U.S. being a high user (74% of all rauwolfia DDDs used in the U.S. were in combination) and Australia having essentially no combinations at all. New Zealand and Britain were intermediate with, respectively, one half and one third of rauwolfia use being in fixed combinations.

The dominant position of rauwolfia derivatives as the mainstay of the NDAH class in the U.S. was declining slowly throughout the early 1970s, but this decline accelerated in 1974 when rauwolfia derivatives were linked (probably wrongly, as it now appears) with breast cancer.[1, 2, 9, 17]

During the 5-year period, the largest differences between Britain and the U.S. in this field narrowed with the approval of a β-blocker and clonidine for use in hypertension in the U.S., after lags of 7 and over 3 years, respectively. Newer drugs such as diazoxide and prazosin appeared in the U.S. with lags of 6 months and 2 years, respectively.

There were still effective drugs unavailable in the U.S., including bethanidine and debrisoquine. Since it has been more than 14 years and 10 years since these drugs were introduced in Britain, however, their current importance is less than it was initially due to the steady evolution of antihypertensive therapy as new drugs have been developed. Nevertheless, as shown above, the influence of these drugs abroad has been substantial as evidenced by the different attitudes toward, and place of adrenergic-neurone–blocking drugs in, the therapy of hypertension.

The differences in antihypertensive therapy that arose between Britain and the U.S. as a result of the greater range of drugs available in Britain are illustrated by the following statement from a paper by Turner and his colleagues who, in 1976, reported their experience with antihypertensive drugs over the previous decade. "In the last 10 years significant side effects have ceased to be a problem, a fact which is attributable to not using methyldopa, guanethidine, rauwolfia or clonidine, to using diuretics, hydralazine or bethanidine for special indications, and relying mainly on the adrenergic-blocking drug debrisoquine, and a beta-blocking agent—initially propranolol, but in recent years, oxprenolol."[19]

The β-blockers are considered in detail in the next section. At this point it is sufficient to note that their antihypertensive action is probably the most important therapeutic discovery of the past 15 years for the treatment of hypertension.

In summary, the largest clinically important discrepancies in the availability of antihypertensive drugs between Britain and the U.S. have diminished as the new drugs, together with some of the older ones, have become available in the U.S.—in all cases after delays which for some drugs are of many years duration. There were still several important drugs available abroad that were not available in the U.S. by the end of 1976, and there is a legacy of different patterns of treatment for hypertension that still lingers.

*The β-blockers.* In awarding the 1976 Lasker prize for Clinical Research to Drs. Raymond Ahlquist and James Black, the respective discoverers of β-receptors and the clinical significance of β-blockade, the Lasker jurors described this class of drugs as one of the most important of the century for the treatment of hypertension and heart disease. The β-blockers have been found to be valuable in an increasing range of disease states. However, as has been the case with antihypertensive and antiarrhythmic drugs, there has invariably been a significant time lag between their approval for

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each given indication in Britain and their approval in the U.S. In addition, the number of β-blockers available in the U.S. is still limited to a single drug, while nine were available in Britain by December, 1976.

The one β-blocker that is available in the U.S. is propranolol. Its initial approval in 1968, 3 years after its approval in Britain, was for a very restricted range of indications—namely, certain types of ventricular arrhythmias, idiopathic hypertrophic subaortic stenosis, and pheochromocytoma. Approval for its use in angina was not obtained in the U.S. for another 5 years (1973) and it was finally approved for hypertension in May, 1976. Thus these last two indications were approved in the U.S. 9 and 12 years after the drug's efficacy in these conditions had first been reported in the world's medical literature, and 7 years in each case after the drug was approved in Britain for the same indications.

During the past 10 years there have been several developments in β-blocker pharmacology, leading to a rapid expansion of the number of β-blockers available abroad and raising the important issue of whether those β-blockers that have appeared since the initial members of the series offer any clinical advantages. There are several areas in which the β-blockers differ among themselves to degrees that are already established as clinically useful. The main areas of difference between members of the series are as follows.

1. Pharmacodynamic properties, including cardioselectivity, intrinsic sympathomimetic activity, membrane (antiarrhythmic) activity, and concomitant α-blocking activity. Differences in these properties can offer theoretical or real advantages to some patient populations in terms of differences in the production of asthma and heart failure and differences in hypotensive and antiarrhythmic efficacy. For example, cardioselective compounds such as metoprolol have less tendency to induce bronchospasm in asthmatic patients and so can be used in certain patients in whom propranolol is contraindicated.

2. Pharmacokinetic properties, such as a longer duration of action. Differences in this area permit, with some of the newer β-blockers for example, a less frequent dosing schedule and hence aid patient compliance, an important feature in the control of diseases such as hypertension.

3. Other properties, such as central nervous system (CNS) side effects. Although not yet well characterized in formal clinical trials, there is enough clinical experience to show real differences in CNS actions among different β-blockers; an early case in point was that practolol was a useful alternative for patients who had intolerable depression or nightmares while on propranolol.

Thus, there are rational pharmacologic and clinical grounds for selection among the different β-blockers, but more comparative studies between the different drugs are needed to identify subpopulations for which different drugs are best suited. This will become more necessary as the range of indications and the number of patients who become candidates for treatment with β-blockers increase.

*Antiarrhythmic drugs*. Since 1968, when the β-blockers were approved for use in arrhythmias, through 1976 no new antiarrhythmics were approved in the U.S. Except for lidocaine, the use of which as an antiarrhythmic was belatedly approved in 1970, no other antiarrhythmic drugs or uses were approved since the introduction of procainamide in 1950. There were, however, five antiarrhythmics exclusively available in Britain, three of which appeared in 1972 to 1976.

As of December, 1976, two antiarrhythmics, namely bretylium tosylate and disopyramide, had been exclusively available in Britain since 1972.* These drugs have been found to be effective for certain patients as well as relatively safe and have been found to be useful alternatives to the presently available antiarrhythmics.

The antiarrhythmic effects of both bretylium and disopyramide were actually first discovered in the U.S. more than 10 years ago. The importance of alternatives to the small number of an-

*Bretylium, which was originally marketed in Britain as an antihypertensive in 1959, was approved in Britain as an antiarrhythmic in December, 1971, and marketed for that purpose in November, 1972. It was therefore not included in the previous study and is not included in the tables of the present study.

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**Table IV.** *Introduction of diuretics, slow-release $K^+$, $Na^+$ supplements, and related drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | Britain | U.S. | Britain | U.S. |
| *Diuretics* | | | | |
| Metolazone (Zaroxolyn) | 5/72 | 11/73 | 18 | |
| Bumetanide (Burinex) | 6/73 | — | | |
| *Potassium supplements* | | | | |
| Slow-K† | 8/65m | 4/75 | 116 | |
| *Sodium supplements* | | | | |
| Slow sodium† | 8/72m | — | | |

*Date of marketing is indicated by "m."

†Listed here but does not satisfy all criteria for inclusion in numerical summaries (Tables I and II).

tiarrhythmics presently available in the U.S. is illustrated by the fact that two of the three main drugs currently used in the U.S. (namely, quinidine and procainamide) may induce very troublesome side effects, while lidocaine, the other mainstay of therapy for serious acute ventricular arrhythmias particularly following a myocardial infarction, is well known to be ineffective in some patients.

Two of the remaining antiarrhythmics that are not available in the U.S., verapamil and perhexiline, are also both effective antianginal drugs, and were initially introduced as such.

Verapamil has been exclusively available in Britain since 1967. It has been found to be as effective as the β-blockers in the symptomatic treatment of angina and has also been found to be very useful in the treatment of supraventricular arrhythmias.

Perhexiline maleate, available in Britain since January, 1976, is a relatively new drug. Its efficacy as an antianginal was first described by Hirshleifer in 1969[12] and since then numerous studies have substantiated this finding. The drug's antiarrhythmic potential was subsequently investigated on the basis of animal and human data which indicated that the drug reduced exercise-induced tachycardia without affecting the resting heart rate. Further studies confirmed perhexiline's antiarrhythmic potential and found it effective, particularly for ventricular arrhythmias. Other actions of perhexiline include a mild diuretic and natriuretic effect. This drug has caused hepatic toxicity in a small proportion of patients.

Mexilitine is a useful new antiarrhythmic that has properties somewhat similar to those of lidocaine, with the additional advantage of being orally active. There is preliminary evidence suggesting that it may reduce postinfarction mortality.

In addition to these several antiarrhythmic drugs that are not available in the U.S., there is one mutually available drug (phenytoin) whose use in arrhythmias is not approved in the U.S. Phenytoin has been found to be effective in some patients in the treatment of digitalis-induced tachyarrhythmias. The drug is extensively used and is recommended by some as the drug of choice in the treatment of these arrhythmias,[29] but has yet to be approved for this indication in the U.S. (NDAs for this indication have been rejected in the U.S. since 1967.)

Considering the number of different etiologies and pathophysiologic mechanisms that induce arrhythmias, it is not surprising that there is no one simple treatment that is consistently effective for arrhythmias. Therefore, the availability of several drugs with differing actions is advantageous in clinical practice to enable treatment to be tailored to each patient, with regard to his arrhythmia, his response to other antiarrhythmic drugs, and his liability to and tolerance of side effects. The ability of the U.S. physician to individualize treatment for arrhythmias compared with his British counter-

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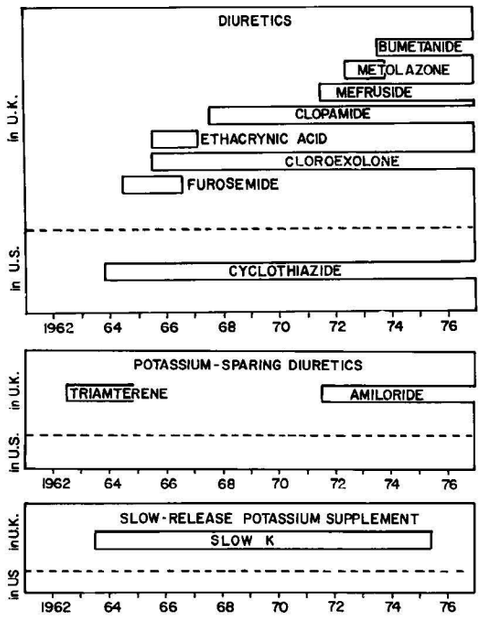


**Fig. 2.** Exclusive availability of diuretics and potassium supplements.

part is noticeably constricted as a result of the smaller number of different drugs available to him.

There is evidence that the narrower range of antiarrhythmic drugs available in the U.S. may have been due, at least in part, to the philosophies of medical reviewing officers in the FDA's Cardiorenal Division. The following passage, which appears as part of a long analysis of the Agency's internal discussions that led to disapprovals of NDAs for phenytoin as an antiarrhythmic from 1967 to 1974 in the FDA's "Commissioner's Report"[18] of October, 1975, is an interesting commentary on the attitudes that prevailed at FDA in the late 1960s toward phenytoin, new antiarrhythmics in general, and practicing physicians.

A physician employed by FDA "expressed dissatisfaction with inadequacies in the medical reports. He also recommended that a new policy be developed to limit the number of anti-arrythmic [sic] drugs on the market. He argued that these agents were complex, unpredictable and paradoxical (i.e., in some circumstances will produce the condition sought to be treated); that there were a variety of agents, ranging from digitalis and quiniline [sic] to beta-blockers to potassium salts, procaine derivatives, and sympathamimetics [sic]"; that "few, if any, physicians are able to be fully knowledgeable concerning the complex pharmacologic variations and characteristics of all these agents"; that unassessable drug effects result if these agents are used concurrently or with other drugs; and that "ideally, a cardiologist should be thoroughly familiar with the characteristics of a minimum of antiarrythmic [sic] agents, such as digitalis, quinidine, and a short acting agent, i.e., lidocaine." He concluded that, although the Federal Food, Drug, and Cosmetic Act does not permit it, he would prefer to require a new product to be proven superior to the digitalis, guinidine [sic], and lidocaine agents before being allowed to market; otherwise, he feared "a 'therapeutic Tower of Babel' which would really increase the dangers to patients."

***Diuretics.*** There were no large clinically important changes in the relative position of each country with respect to diuretics. The strongly potassium-sparing diuretic, amiloride, is still available only in Britain. However, with the introduction of slow-release potassium supplements into the U.S. 12 years after they were introduced in Britain, the overall disparity in this field became smaller than in 1971 (Table IV and Fig. 2).

***Respiratory drugs.*** The bronchoselective $\beta$-adrenergic bronchodilators metaproterenol and terbutaline were approved in the U.S. during the period 1972 to 1976, 11 years and 3 years after their introduction in Britain. This eliminated the clinically important gap that had existed previously in the field of bronchoselective bronchodilators (Table V and Fig. 3).

Two important drugs for asthma, cromolyn sodium and beclomethasone (inhaled), were also introduced in the U.S., after lags of 5 years and 3½ years. This clinically important gap is also closed now, although cromolyn remains exclusively available in Britain for certain other uses (e.g., for nasal insufflation in allergic rhinitis and for allergic conjunctivitis).

The concept of administering steroids as an aerosol is not entirely new, and in fact aerosolization of hydrocortisone, prednisone, and dexamethasone has been used in the past with therapeutic effects in many patients with asthma. However, when used in effective doses, most of these preparations were sufficiently absorbed from the bronchial tree to induce suppression of adrenal function. This is in contrast

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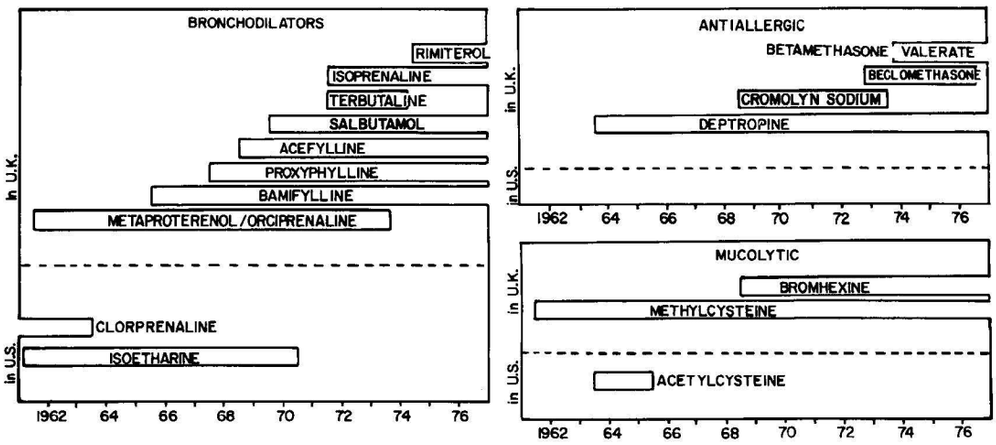


**Fig. 3.** Exclusive availability of respiratory drugs.

**Table V.** *Introduction of respiratory drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | Britain | U.S. | Britain | U.S. |
| *Bronchodilators* | | | | |
| Metaproterenol/orciprenaline (Alupent) | 6/62m | 7/73 | 133 | |
| Terbutaline (Bricanyl) | 6/71 | 3/74 | 33 | |
| Rimiterol (Pulmadil) | 6/74m | — | | |
| *Antiallergics* | | | | |
| Cromolyn sodium (Intal, U.K., U.S.; Aarane, U.S.) | 12/68m | 6/73 | 54 | |
| Beclomethasone dipropionate (Becotide inhaler, U.K.; Vanceril, U.S.) | 11/72m | 5/76 | 42 | |
| Betamethasone valerate† (Bextasol inhaler) | 9/73m | — | | |

*Date of marketing is indicated by "m."

†Not NCE but important new dose form (inhaler). This was not included in the numerical summaries (Tables I and II).

to beclomethasone dipropionate and betamethasone valerate which have been found to be highly effective but to date have not been found to induce appreciable suppression of hypothalamic/pituitary/adrenal function. With the use of these aerosolized steroid preparations in therapeutic doses, most steroid-dependent asthmatics can substantially reduce or eliminate the need for orally administered steroids.

Side effects from these preparations have not been serious, the main one of importance being candida infection of the larynx and pharynx, which appears to be dose-related. To date there have been few reports of serious pulmonary or systemic candida infections. The development of these new aerosolized steroid preparations is a major advance in the treatment of asthma and has already had a significant impact on the therapeutic regimen for this disease.

In summary, after long lag periods, the main gaps in the respiratory field were eliminated by the introduction to the U.S. of bronchoselective bronchodilators, and of cromolyn and beclomethasone. Bromhexine continues to be exclusively available in Britain, showing modest utility as a sputum liquefier in chronic bronchitis.

***Anti-infective drugs.*** Although significant anti-infective drugs were not available in the U.S., these were relatively few. The introduc-

been serious, the main one of importance being candida infection of the larynx and pharynx, which appears to be dose-related. To date there have been few reports of serious pulmonary or systemic candida infections. The development of these new aerosolized steroid preparations is a major advance in the treatment of asthma and has already had a significant impact on the therapeutic regimen for this disease.

In summary, after long lag periods, the main gaps in the respiratory field were eliminated by the introduction to the U.S. of bronchoselective bronchodilators, and of cromolyn and beclomethasone. Bromhexine continues to be exclusively available in Britain, showing modest utility as a sputum liquefier in chronic bronchitis.

***Anti-infective drugs.*** Although significant anti-infective drugs were not available in the U.S., these were relatively few. The introduc-

**Table VI.** *Introduction of anti-infective drugs, 1972 to 1976*

| | *Date of introduction** | | *Lead in months* | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *Penicillins* | | | | |
| Amoxicillin (Amoxil) | 2/72 | 1/74 | 23 | |
| Carbenicillin indanyl sodium (Geocillin) | — | 10/72 | | |
| Carfecillin (Uticillin) | 9/74m | — | | |
| Talampicillin (Talpen) | 10/75m | — | | |
| Ticarcillin disodium (Ticar) | — | 11/76 | | |
| *Cephalosporins* | | | | |
| Cephradine (Eskacef, U.K.; Velosef, U.K., U.S.) | 9/72 | 8/74 | 23 | |
| Cephazolin (Kefzol, U.K.; Ancef, U.S.; | 6/74m | 10/73 | | 8 |
| Cephapirin (Cefadyl) | — | 3/74 | | |
| Cephacetrile (Celospor) | — | 9/74 | | |
| *Others* | | | | |
| Co-trimoxazole (Septrin, U.K.; Bactrim, U.K., U.S.; Septra, U.S.) | 10/68m | 7/73 | 57 | |
| Minocycline (Minocin) | 7/72 | 6/71 | | 13 |
| Spectinomycin (Trobicin) | 9/72 | 6/71 | | 15 |
| Oxolinic acid (Prodoxol, U.K.; Utibid, U.S.) | 6/74m | 7/75 | 13 | |
| Tobramycin (Obracin, U.K.; Nebcin, U.S.) | 9/74m | 6/75 | 9 | |
| Sulfacytine (Renoquid) | — | 9/75 | | |
| Amikacin (Amikin) | 12/76m | 7/76 | | 5 |
| *Antifungals* | | | | |
| Clotrimazole (Canesten, U.K.; Lotrimin, U.S.) | 11/72 | 2/75 | 27 | |
| Miconazole nitrate (Daktarin, U.K.; Monistat, U.K., U.S.; Micatin, U.S.) | 6/74m | 1/74 | | 5 |
| *Anthelmintics* | | | | |
| Mebendazole (Vermox) | 9/76m | 6/74 | | 27 |
| *Antivirals* | | | | |
| Idoxuridine (Herpid) | 4/74m | — | | |
| Vidarabine (Vira-A) | — | 11/76 | | |

*Date of marketing is indicated by "m."

tion of co-trimoxazole in the U.S., 5 years after its marketing in Britain, substantially cleared the backlog of useful drugs in this category that were not available in the U.S. Two newer antibiotics, spectinomycin and minocycline, were introduced earlier in the U.S. while others, such as tobramycin and amikacin, were introduced more or less simultaneously in both countries (Table VI and Fig. 4).

In the field of penicillins and cephalosporins, there were some minor advances in which both countries shared equally; at the end of 1976 the U.S. had two cephalosporins not available in Britain. Fusidic acid, which was discussed in the earlier papers, is still not available in the U.S.

In the field of antiparasitic therapy, there are several drugs marketed exclusively in Britain. However, some of these are available in the U.S. through the Center for Disease Control, under INDs that permit therapeutic use.

***Anticancer and immunosuppressive drugs.*** In the earlier report, this was identified as an area in which the U.S. and Britain were approximately comparable with equal numbers of new drugs exclusively available in each country and no prominent clinical discrepancies on either side (Table VII and Fig. 5).

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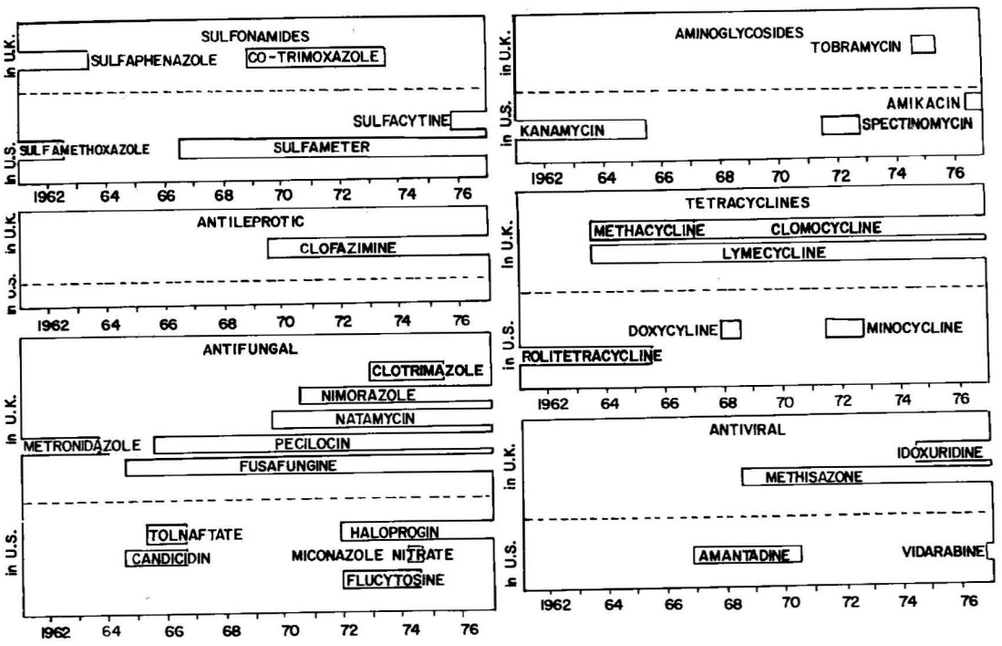


**Fig. 4A.** Exclusive availability of anti-infective drugs.

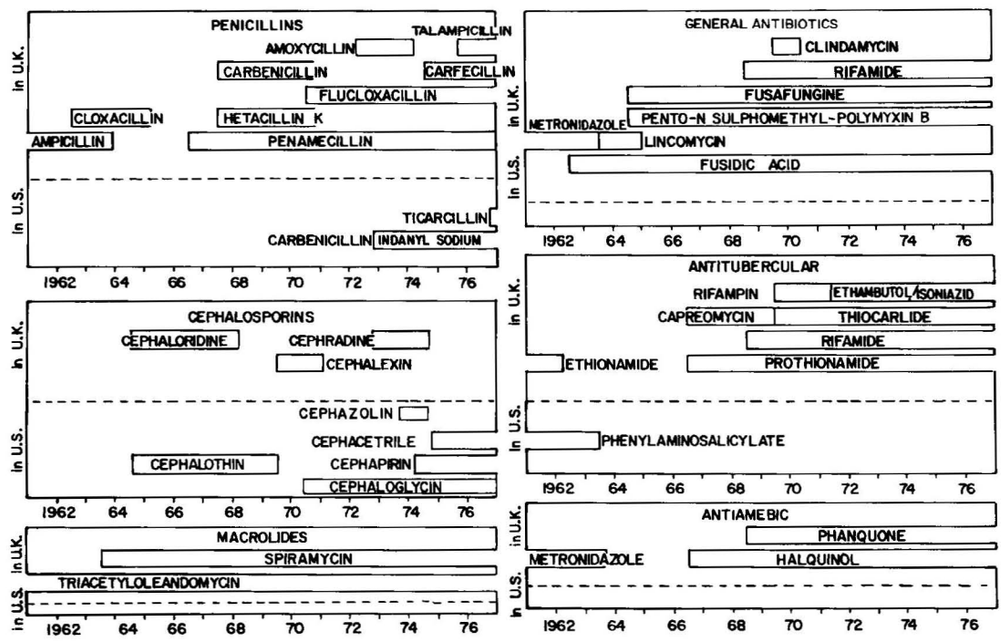


**Fig. 4B.** Exclusive availability of anti-infective drugs.

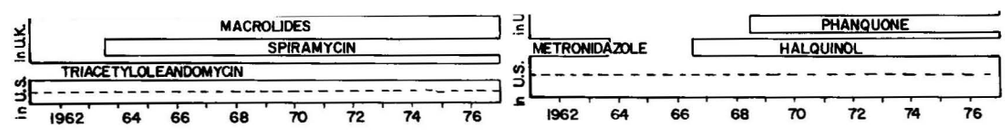


**Fig. 4B.** Exclusive availability of anti-infective drugs.

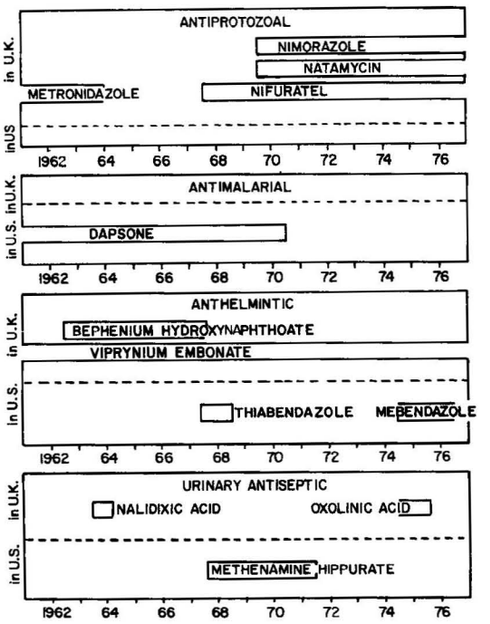


**Fig. 4C.** Exclusive availability of anti-infective drugs.

This pattern was maintained. The therapeutic consequences of the differences that existed in this 5-year period need to be explored in more detail, but do not appear to be major.

***Centrally acting drugs.*** Many more new centrally acting drugs were introduced exclusively into Britain from 1972 through 1976 than into the U.S. The drugs in this area are best considered by therapeutic subcategory (Table VIII and Fig. 6).

*Major tranquilizers.* A larger number of drugs in this category were exclusively available in Britain than in the U.S. The available evidence does not point to any outstandingly good or bad drugs exclusively available in either country.

Flupenthixol, a major tranquilizer, is exclusively available in Britain. It has been shown to be effective in the treatment of schizophrenia and major psychosis. When used in low doses it also induces an antidepressant effect with less evidence of side effects than other widely used antidepressant drugs. Flupenthixol is also available in the long-acting depot injectable form. A somewhat similar drug in depot form, fluphenazine decanoate, is available in the U.S.

Molindone is an indole derivative and represents a new class of psychotropic drug structurally unrelated to the phenothiazines. It is exclusively available in the U.S. Molindone has been reported to possess definite antipsychotic and questionable antidepressant properties. Even though this drug is considered to be a useful alternative to phenothiazines, controlled clinical trials have not yet demonstrated any advantages over available phenothiazines either in terms of efficacy or safety. Molindone has a slow onset of action.

Loxapine is a major tranquilizer that has been exclusively available in the U.S. since 1975. Loxapine, a dibenzoxazepine, is a new chemical entity (NCE) offered as an alternative for the treatment of schizophrenia. As with molindone, clinical studies have not demonstrated any definite superiority over currently used phenothiazines; the side effects have also been similar to phenothiazines. However, the utility of having a wide range of drugs available to enable physicians to tailor drugs to individual patients is a very important consideration in this therapeutic category.

*Minor tranquilizers.* Relatively more minor tranquilizers were available in Britain than in the U.S. The available data do not, however, indicate any noteworthy drugs exclusively available in either country.

*Antidepressants: Non-monoamine oxidase (MAO) antidepressants.* There were 12 non-MAO antidepressants exclusively available in Britain, half of them introduced in 1972 to 1976; there were none exclusively available in the U.S. The major tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, imipramine, desipramine, and doxepin, were introduced at nearly the same time in both countries. The newer drugs available in Britain, such as clomipramine, dibenzepin, butriptyline, and maprotiline, while effective in the treatment of depressive disorders, have not yet been demonstrated to have overall advantages in terms of efficacy over the more familiar earlier TCAs. Some very useful differences in toxicity and side effects have, however, been demonstrated.

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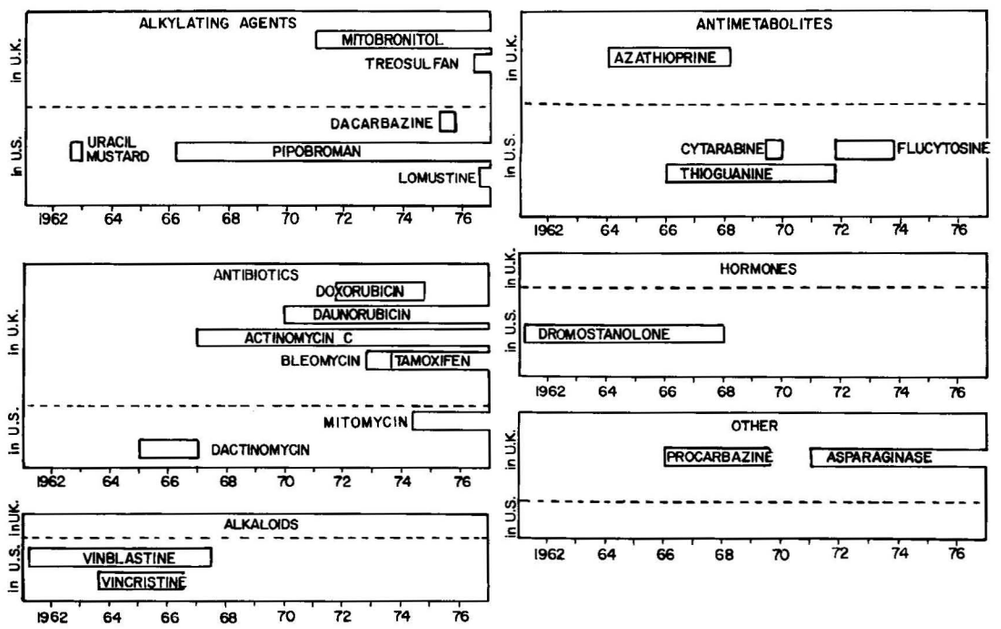


**Fig. 5.** Exclusive availability of anticancer drugs.

**Table VII.** *Introduction of anticancer drugs, 1972 to 1976*

| *Drug* | *Date of introduction** | | *Lead in months* | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *Anticancer* | | | | |
| Thioguanine (Lanvis, U.K.; Thioguanine Tabloid, U.S.) | 12/71 | 1/66 | | 71 |
| Flucytosine (Ancobon) | 9/73 | 11/71 | | 22 |
| Doxorubicin (Adriamycin) | 11/71m | 8/74 | 33 | |
| Bleomycin (Bleomycin) | 9/72 | 7/73 | 10 | |
| Tamoxifen (Nolvadex) | 7/73 | — | | |
| Mitomycin (Mutamycin) | — | 5/74 | | |
| Dacarbazine (DTIC-Dome) | 10/75m | 5/75 | | 5 |
| Treosulfan (treosulfan) | 5/76m | — | | |
| Lomustine (CeeNU) | — | 8/76 | | |

*Date of marketing is indicated by "m."

Viloxazine has the extremely important attribute of relative safety in acute overdosage. This is a crucial feature of a drug designed for a disease in which attempts at suicidal drug overdose are common and for which the mainstay of drug therapy in the U.S. (the tricyclic family of compounds) is potentially cardiotoxic. Viloxazine has now been available in Britain for 3 years and reports of severe toxicity are rare. Doses of several grams of viloxazine in suicide attempts have been closely followed and little or no cardiac toxicity has been reported. This low toxicity could make viloxazine as important a safety advance as the benzodiazepines were in the field of sedative-hypnotics, since, with the advent of benzodiazepines and the resultant lowering of mortality from the barbiturates they replaced, poisoning by TCAs has become one

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**Table VIII.** *Introduction of centrally acting drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *Major tranquilizers* | | | | |
| Fluphenazine decanoate† (Modecate, U.K.; Prolixin Decanoate, U.S.) | 12/68m | 6/72 | 42 | |
| Flupenthixol (Depixol) | 2/72 | — | | |
| Benperidol (Anquil) | 4/73 | — | | |
| Molindone (Moban) | — | 1/74 | | |
| Loxapine (Loxitane) | — | 2/75 | | |
| Fluspirilene (Redeptin) | 6/75m | — | | |
| *Minor tranquilizers* | | | | |
| Clorazepate (Tranxene) | 2/73 | 6/72 | | 8 |
| Lorazepam (Ativan) | 7/72 | — | | |
| Prazepam (Verstran) | —‡ | 12/76 | | |
| *Antidepressants* | | | | |
| Viloxazine (Vivalan) | 11/74m | — | | |
| Butriptyline (Evadyne) | 2/75m | — | | |
| Maprotiline (Ludiomil) | 3/75m | — | | |
| Mianserin (Bolvidon) | 5/76m | — | | |
| *Hypnotics* | | | | |
| Flurazepam (Dalmane) | 10/73 | 4/70 | | 42 |
| *Antiemetics, Antimigraine* | | | | |
| Clonidine (Dixarit, U.K.; Catapres, U.S.) | 8/71m | —§ | | |
| Benzquinamide (Emete-Con) | — | 3/74 | | |
| Pizotifen (Sanomigran) | 10/75m | — | | |
| *Anticonvulsants* | | | | |
| Clonazepam (Rivotril, U.K.; Clonopin, U.S.) | 8/74m | 6/72 | 10 | |
| Sodium valproate (Epilim) | 11/74m‖ | — | | |
| *Muscle relaxants* | | | | |
| Baclofen (Lioresal) | 6/72 | — | | |
| Dantrolene (Dantrium) | 4/73 | 1/74 | 9 | |
| *Anorectics* | | | | |
| Fenfluramine (Ponderax) | 10/63m | 6/73 | 116 | |
| Mazindol (Teronac, U.K.; Sanorex, U.S.) | 2/73 | 6/73 | 4 | |
| Clortermine (Voranil) | — | 6/73 | | |
| *Antiparkinsonian* | | | | |
| Benapryzine (Brizin) | 7/73 | — | | |
| Levodopa/carbidopa (Sinemet) | 9/73 | 5/75 | 20 | |
| Levodopa/benserazide (Madopar) | 10/74m | — | | |

*Date of marketing is indicated by "m."

†Long-acting dose form. This compound is excluded from the numerical summaries (Tables I and II).

‡Approved in Britain but not yet available.

§Not approved for migraine in the U.S. This drug is included in the numerical summaries in the cardiovascular area.

‖Approved in 1972 for hospital use only.

of the major self-poisoning emergencies in medicine.

Mianserin, an antidepressant recently introduced in Britain but not available in the U.S., represents a new class of drugs. It is a piperazino-azepine compound not structurally related to either tricyclics or MAO inhibitors. Controlled clinical trials have demonstrated mianserin to be as effective as amitriptyline in primary depressive illness, but there was a striking difference in side effects between mianserin and amitriptyline. Mianserin was followed by a

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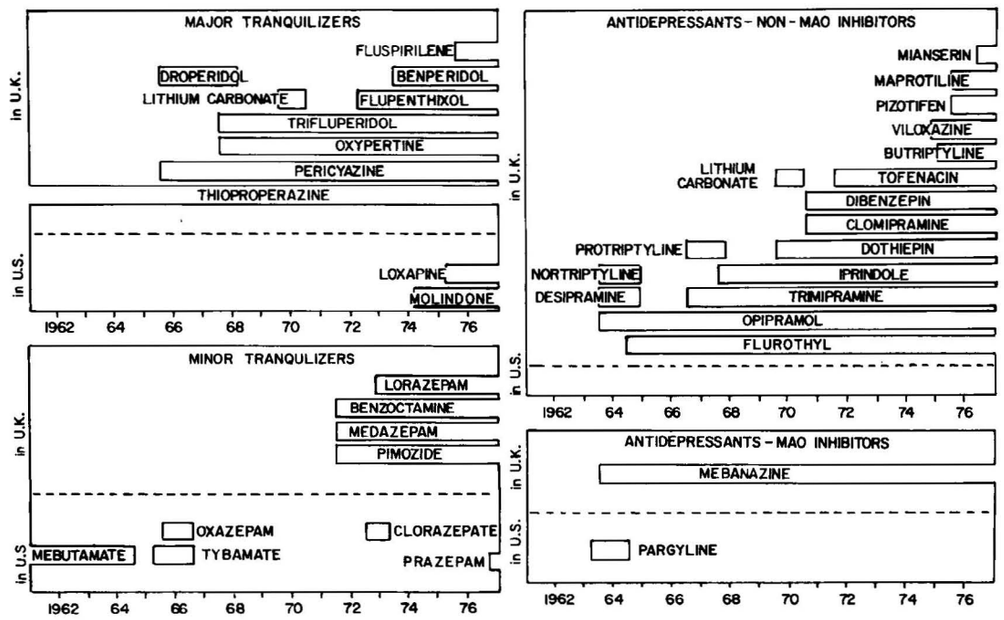


**Fig. 6A.** Exclusive availability of CNS drugs.

lower incidence of total reported side effects, indicating that it not only had relatively fewer significant side effects but that it also improved those symptoms of the illness which resembled or were confused with drug side effects; in this respect mianserin is clearly superior to amitriptyline. Unlike TCAs, mianserin is devoid of side effects due to interaction with adrenergic and cholinergic systems. The mode of action of mianserin is still obscure. Even though at higher doses it inhibits the uptake of serotonin, in doses used to treat depression the drug does not influence the reuptake of amines nor is it an MAO inhibitor. The apparent lack of effect on amines is difficult to reconcile with the biogenic amine theory of affective disorders. It is likely that elucidation of its mode of action will throw fresh light on the chemical pathology of affective disorders.

*Antidepressants. MAO inhibitors.* No new MAO inhibitor was introduced in either country since 1963-1964.

*Antiparkinsonian drugs.* Levodopa, which was introduced in 1971 in both countries for the treatment of parkinsonism, has significantly altered the therapy of this disease.

Concurrent administration of levodopa with a decarboxylase inhibitor allows a greater proportion of the administered levodopa to reach the target receptor sites in the nigrostriatum. Carbidopa is the only approved dopa-decarboxylase inhibitor available in the U.S. It is available as a combination tablet with levodopa in a 1:10 ratio (Sinemet). A 2-year British lead in the approval of carbidopa and also the exclusive availability of another decarboxylase inhibitor (benserazide) in combination with levodopa (Madopar) in Britain are noteworthy. Benserazide in combination with levodopa is as effective as carbidopa with levodopa.

Amantadine was first introduced in the U.S. in 1966 as an antiviral agent against Asian $A_2$ influenza virus. Even though it was available in the U.S. 4 years earlier than in Britain, its use in parkinsonism was approved only in 1973, i.e., 3 years after it became available in Britain for this indication.

*Muscle relaxants: Centrally acting.* Tetrabenazine is exclusively available in Britain. It is a centrally acting drug having certain pharmacologic effects similar to those of reserpine, but its action is more rapid in onset and shorter in duration. It causes depletion of serotonin and

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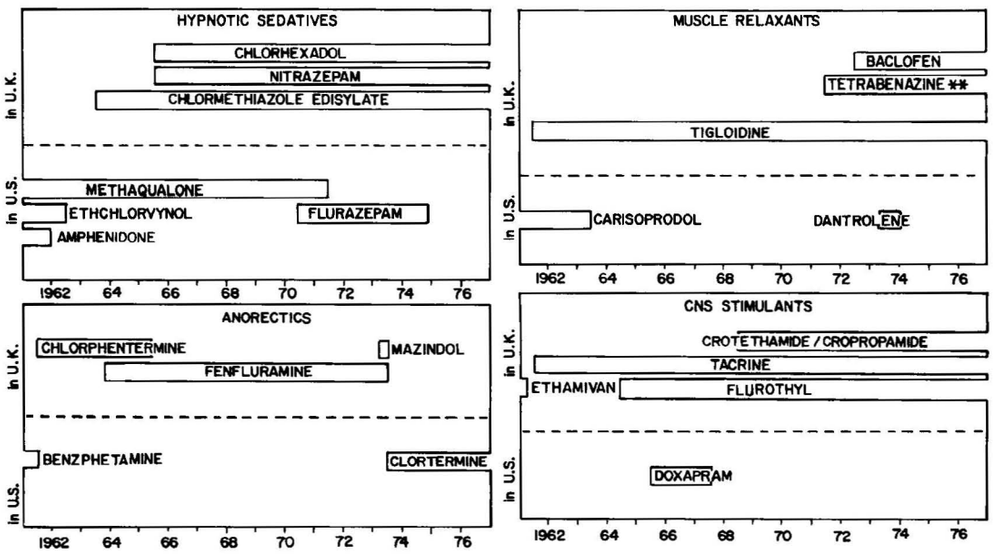


**Fig. 6B.** Exclusive availability of CNS drugs. **This drug was approved earlier for a different indication.

norepinephrine in the brain but, unlike reserpine, it appears to have little effect on the concentration of these monoamines in peripheral tissues. Tetrabenazine has been used in the treatment of dyskinesias and extrapyramidal disorders and there is also some evidence that it can be effective in Huntington's chorea.

Baclofen, a centrally acting derivative of gamma-aminobutyric acid which has muscle relaxant properties, was also exclusively available in Britain through 1976. The relief of symptoms of spasticity by baclofen has been documented in several clinical trials. Baclofen, however, shows differences in therapeutic responses in different types of neurologic lesions, patients with multiple sclerosis and spinal injuries responding better than those with cerebral lesions.

*Muscle relaxants: Direct acting.* Dantrolene represents a new class of drugs that have a direct relaxant action on skeletal muscle. This drug was marketed in the U.S. a year earlier than in Britain. It produces relaxation and reduces contraction of skeletal muscle by a direct action on excitation-contraction coupling, possibly by decreasing the amount of calcium released from the sarcoplasmic reticulum. Dantrolene provides significant and sustained reduction of spasticity and has been shown to improve functional capacity in patients with paraplegia, hemiplegia and multiple sclerosis. Tolerance to its therapeutic effect does not appear to develop, but the drug tends to induce generalized muscle weakness that can be detrimental to functional improvement. There are some recent reports of hepatotoxic reactions. Although the incidence of such a reaction is low (0.1 to 1.8%), it can be serious. Dantrolene may represent a significant advance in the medical management of spastic disorders.

*Anorectics.* A new class of anorectics without amphetamine-like and certain other side effects was brought to the U.S. in 1973 with the introduction of fenfluramine, clortermine, and mazindol. Of these, fenfluramine had been available in Britain for about 10 years.

A 10-year British lead in the approval of fenfluramine is noteworthy. Fenfluramine is a phenylethylamine that lacks certain undesirable features of the amphetamines. In the treatment of obesity fenfluramine has efficacy comparable to that of amphetamines. Although dependence can be demonstrated after chronic use, the drug has less potential for abuse than amphetamines. Fenfluramine has been shown not to antagonize the actions of antihypertensive agents, an im-

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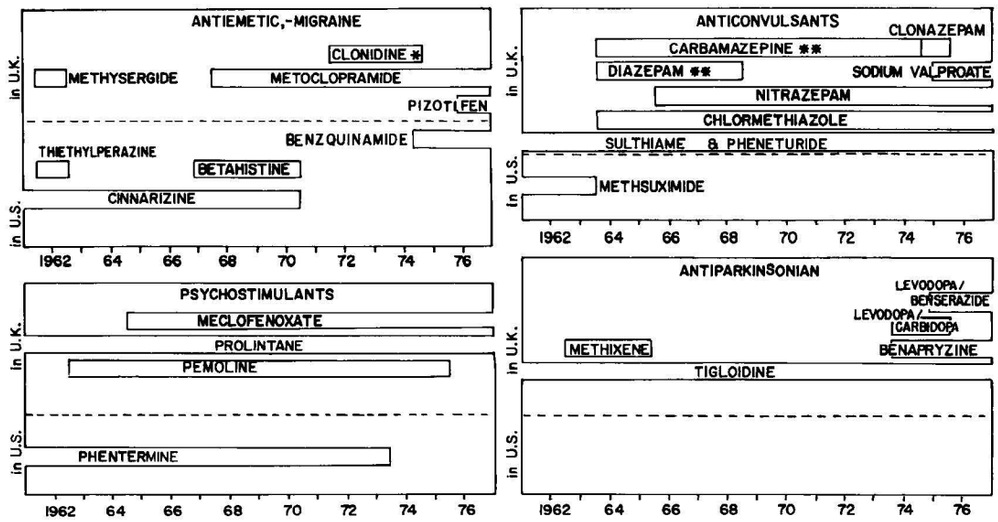


**Fig. 6C.** Exclusive availability of CNS drugs. *This drug has not been approved for migraine in the U.S. **This drug was approved earlier for a different indication.

portant consideration in patients who are both obese and hypertensive.

Clortermine is another phenylethylamine similar to fenfluramine, with similar pharmacologic properties. It is now exclusively available in the U.S.

Mazindol, an imidazolethylamine and therefore the only anorectic that is not a phenylethylamine, is believed to exert its effect in part by facilitating electrical activity in the septal area of the brain. Mazindol was marketed in the U.S. in 1973, a year earlier than in Britain. It has similar anorectic activity without the side effects or, at least as experienced so far, the abuse potential of the amphetamine anorectics.

*Anticonvulsants.* From 1960 through 1976 a total of 11 anticonvulsant drugs were approved for marketing in the U.S. or Britain.[24] Two of these (sodium valproate and clonazepam) appeared after 1972 (valproate being exclusively available and clonazepam mutually available), while the use of one already marketed drug (carbamazepine) was approved for epilepsy in the U.S. some 11 years after its marketing in Britain for this purpose.

Considering all of the 11 drugs, there were substantial differences between Britain and the U.S. in the drugs available for epilepsy by the end of 1976. Five of the drugs were introduced exclusively in Britain, and 6 were introduced in both countries. None was exclusively introduced into the U.S. Of the 6 drugs introduced into both countries, one (methsuximide) was available first in the U.S., but this drug is similar to ethosuximide, which was already available in both countries. The other 5 mutually available drugs all became available (or were approved for epilepsy) earlier in Britain than in the U.S., in some cases by many years. The 5 antiepileptic drugs exclusively available in Britain were pheneturide, sulthiame, chlormethiazole, nitrazepam, and valproate.

Most of the drugs shown here were described in our earlier study. Sulthiame and pheneturide are valuable drugs in some patients, while nitrazepam is still one of the major drugs for childhood seizures.

Of the drugs introduced during the 1972 to 1976 period, sodium valproate is of particular interest. It was introduced in Britain in 1972 and became a treatment of choice for generalized epilepsy, partly because of its effectiveness in some patients in whom standard therapy had failed, and partly because it lacks the marked CNS-depressant side effects of the other antiepileptic drugs. The importance of valproate is exemplified by the fact that the Congressionally-instituted National Commis-

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**Table IX.** *Introduction of anesthetic drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months† | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *General anesthetics* | | | | |
| Alphaxalone/alphadolone (Althesin) | 3/72 | — | | |
| Trifluoroethyl difluoromethyl ether (Ethrane) | — | 8/72 | | |
| *Local anesthetics* | | | | |
| Bupivacaine (Marcain, U.K.; Marcaine, U.S.) | ?/68m | 10/72 | (52) | |
| Etidocaine (Duranest) | — | 8/76 | | |
| *Neuromuscular blocking* | | | | |
| Pancuronium (Pavulon) | ?/68m | 10/72 | (52) | |
| Fazadinium (Fazadon) | 11/76m | — | | |

*Date of marketing is indicated by "m."

†For those British drugs for which the month is not known, calculation of the lead was based on a June date and these values are given in parentheses. These estimates may thus be in error by up to six months in either direction.

sion for the Control of Epilepsy and Its Consequences devoted an entire day's meeting in April, 1977, to a consideration (which involved interrogation of industry and FDA representatives) of why there was at that time still no early prospect for its marketing in the U.S. During the course of these hearings it developed that the drug had been successfully used in Britain and Europe in over 100,000 patients, and its benefit-to-risk ratio was well characterized. Submission of an NDA in the U.S. was awaiting the completion of clinical trials in a few score American patients. The staff of the Commission estimated that the absence of this one drug on the U.S. market was subjecting American patients to approximately 1,000,000 unnecessary seizures a year at a cost of approximately $200,000,000 a year.

Thus from 1960 through 1976 all but one of the 11 drugs introduced for epilepsy in the U.S. or Britain were introduced first in Britain (by margins of up to 11 years, based on date of approval for antiepileptic usage); and half of the drugs were not yet available in the U.S. Those drugs unavailable included important major antiepileptic drugs such as sodium valproate. They also included drugs such as nitrazepam and sulthiame that, while not of great importance to large numbers of epileptics, are known to be uniquely effective in some patients.

*Antimigraine drugs.* From 1971 through 1976 one new drug, pizotifen, became available for prophylactic use in the treatment of migraine in Britain. It was not available in the U.S. While it appears not to be as effective as methysergide, it is safer since it has not been implicated in causing side effects as serious as retroperitoneal fibrosis. There is a significant rate of response to pizotifen, and it can therefore serve as a useful drug with which to initiate prophylactic therapy.

Clonidine is also approved for the treatment of migraine in Britain in a smaller dose form than for hypertension. Clonidine and propranolol are both available in the U.S. but are not approved for migraine, in which they have been shown to be very useful in some patients.

In summary, many more drugs are available in Britain than in the U.S. that act on the central nervous system. In some clinical subcategories, such as the antiepileptics there are clear advantages to patients in Britain for whom there are available newer, more effective, or less toxic drugs. In some areas, such as minor tranquilizers, no clinical significance results from the differences; in other areas, such as antidepressants, new structural classes are available that are of theoretical interest, but whether a major clinical advantage exists in terms of efficacy is not yet known. In terms of safety and side effects, however, there are clear advantages to some of the drugs available abroad but not in the U.S.

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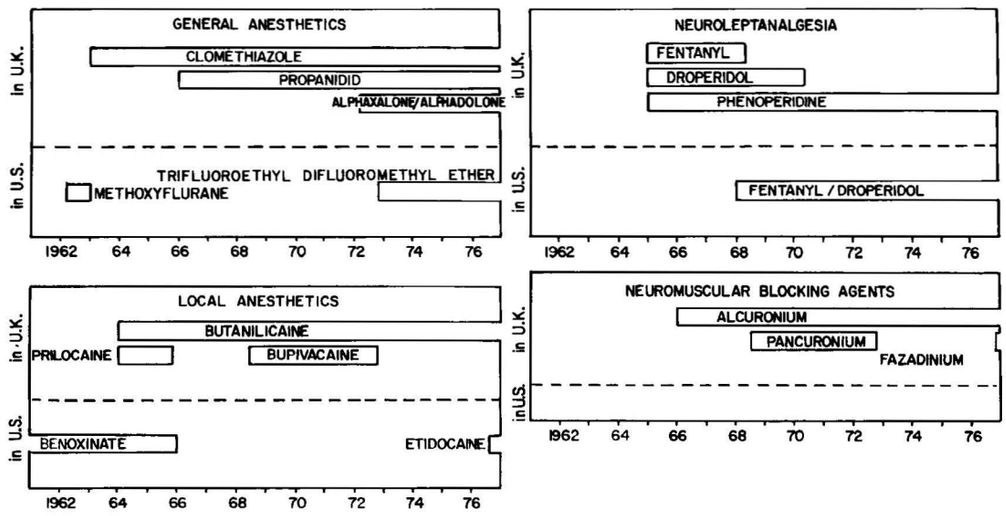


**Fig. 7.** Exclusive availability of anesthetic drugs.

esthetics, the range of drugs available exclusively in Britain was widened by the exclusive introduction there of the short-acting intravenous anesthetic alphaxalone, alphadolone. Conversely, the inhalational anesthetic enflurane was introduced exclusively in the U.S. (Table IX and Fig. 7).

In the area of neuromuscular blocking drugs, pancuronium was introduced to the U.S. after a lag of approximately 4 years; another short-acting competitive drug is now available in Britain.

***Analgesic and related drugs.*** Six new nonsteroidal anti-inflammatory drugs appeared in the 5-year period. This brought the number that appeared since 1962 to 11: 5 of these were available in both countries, 5 were available exclusively in Britain, and one was available exclusively in the U.S. In general, the drugs are fairly similar in efficacy, at least in terms of the ceiling effect if the dose is increased sufficiently. The main advantages that can be claimed for some of the newer members are different pharmacokinetics (e.g., allowing less frequent and therefore more convenient dosing schedules) and a diminished incidence—or at least a different spectrum—of side effects compared with the older alternatives such as aspirin or phenylbutazone. With some of these newer drugs an improved therapeutic ratio has indeed been claimed, but the type of proof available is in most cases not yet rigorous and there are relatively few comparisons of the various drugs in specific subpopulations of patients. In my opinion, the range of drugs now available (and the expanded range that is on the horizon) would be better justified if subgroups of patients were identified in whom specific advantages for one or another drug could be shown. In view of the known needs of different patients for different drugs, and of the clinical experience with existing compounds to date, this should not be too difficult but it has not yet been done for most of these drugs (Table X and Fig. 8).

In the case of narcotics and narcotic antagonists, there was a British lag in the introduction of the pure narcotic antagonist, naloxone over 2 years after its introduction in the U.S.

***Gastrointestinal drugs.*** This is an area in which, as shown in our original papers, there were several interesting drugs available in Britain but not in the U.S. In the field of peptic ulcer by the end of 1976 the U.S. lacked the only two drugs that have been unequivocally shown to exert a healing effect on peptic ulcer: carbenoxolone (introduced in Britain in 1963) and cimetidine (the first $H_2$ antagonist; introduced there in 1976) (Table XI and Fig. 9).

Gastrointestinal drugs that had previously been available exclusively in Britain, such as

frequent and therefore more convenient dosing schedules) and a diminished incidence—or at least a different spectrum—of side effects compared with the older alternatives such as aspirin or phenylbutazone. With some of these newer drugs an improved therapeutic ratio has indeed

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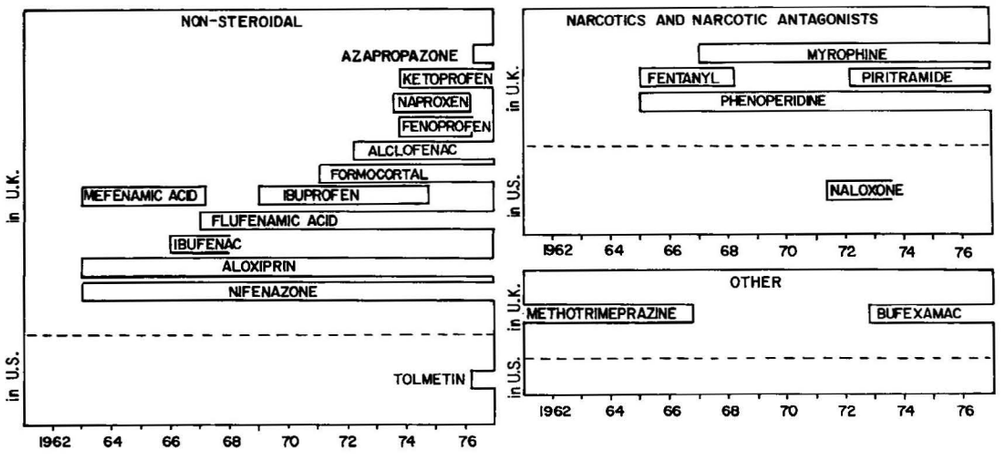


**Fig. 8.** Exclusive availability of analgesic and anti-inflammatory drugs.

**Table X.** *Introduction of analgesic and related drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months | |
|---|---|---|---|---|
| | *Britain* | *U.S.* | *Britain* | *U.S.* |
| *Nonsteroidal analgesics and anti-inflammatories* | | | | |
| Ibuprofen (Brufen, U.K.; Motrin, U.S.) | 2/69m | 9/74 | 67 | |
| Alclofenac (Prinalgin) | 3/72m | — | | |
| Naproxen (Naprosyn) | 7/73 | 3/76 | 32 | |
| Ketoprofen (Orudis) | 9/73 | — | | |
| Fenoprofen (Fenopron, U.K.; Nalfon, U.S.) | 10/73 | 3/76 | 29 | |
| Tolmetin (Tolectin) | — | 3/76 | | |
| Azapropazone (Rheumox) | 4/76m | — | | |
| *Narcotic type and narcotic antagonists* | | | | |
| Naloxone (Narcan) | 7/73 | 4/71 | | 27 |
| Piritramide (Dipidolor) | 2/72m | — | | |
| *Others* | | | | |
| Bufexamac (Feximac), topical | 12/72 | — | | |

*Date of marketing is indicated by "m."

lactulose and pentagastrin, were introduced into the U.S. after lags of more than 6 years. In other respects the status of this area was unchanged, with several other interesting but probably not vital drugs continuing to be available abroad.

## Discussion and conclusions

In the previous study covering the decade through 1971, we found large differences of clinical importance between the U.S. and Britain in the therapeutic fields represented by cardiovascular, diuretic, respiratory, anti-infective, and gastrointestinal drugs. This study shows that in the subsequent 5 years, the relationship changed perceptibly—not so much in the relative numbers of new drugs that became available (in which Britain still substantially exceeded the U.S.), but in the narrowing of the most obvious therapeutic differences between the two countries.

In the anti-infective area, by the end of 1976 there was little difference between the two countries; in fact, some useful new antibiotics

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In the anti-infective area, by the end of 1976 there was little difference between the two countries; in fact, some useful new antibiotics

**Table XI.** *Introduction of gastrointestinal drugs, 1972 to 1976*

| Drug | Date of introduction* | | Lead in months† | |
|---|---|---|---|---|
| | Britain | U.S. | Britain | U.S. |
| *Peptic ulcer* | | | | |
| Cimetidine (Tagamet) | 11/76 | — | | |
| *General* | | | | |
| Lactulose (Duphalac, U.K.; Cephulac Syrup, U.S.) | 3/69m | 3/76‡ | 84 | |
| Hydrotalcite (Altacite) | 11/72 | — | | |
| Loperamide (Imodium) | 5/75m | 12/76 | 19 | |
| *Diagnostics* | | | | |
| Pentagastrin (Peptavlon) | ?/67m | 7/74 | (85) | |

*Date of marketing is indicated by "m."

†For those British drugs for which the month is not known, calculation of the lead was based on a June date and these values are given in the parentheses. These estimates may thus be in error by up to six months in either direction.

‡Approved only for portocaval encephalopathy in U.S.

were approved earlier in the U.S. than in Britain. In the respiratory field, after substantial delays the most important differences were essentially eliminated. The remaining fields in which the U.S. was still behind Britain with respect to therapeutically important drugs by December, 1976, included the cardiovascular area, peptic ulcer, and epilepsy*; some of the discrepancies in these areas had been present for over 10 years. In other areas only scattered differences were observed which, while mostly in the direction of a British lead, did not form as strong and consistent patterns as before. It should be noted, however, that the present clinical interpretations of the differences between the countries deal only with the most obvious differences, and further examination of more subtle properties of the drugs presently not available in the U.S. would be likely to increase the interpreted clinical significance of these differences.

The reasons for the narrowing of the large differences between Britain and the U.S. are many and the relative importance of each cannot be completely determined. It should be clearly understood that the patterns we have described here are the result of both regulatory and industrial policies and actions (or lack of them) and that the existence of a lag does not imply one cause over another. Although there are cases of a clear delay because of a firm's failure to file an Investigational New Drug (IND) or New Drug Application (NDA), as well as other cases where there has obviously been excessive regulatory inhibition, many more cases involve a complex mixture of the two causes which cannot be resolved without complete knowledge of the facts and assessment of the opposing arguments. Thus, does a delay in filing (or failure to file) an NDA mean that a firm is slothfully heedless of future profits or that it is diligently accumulating what it perceives to be enough data to satisfy FDA's high standards? Such determinations were beyond the scope of this study.

Among the regulatory factors contributing to the convergence in patterns of drug availability are changes in policies in both the U.S. and Britain. In certain respects by 1976 U.S. drug regulatory policies had become more consistent with current world standards of professional and scientific thought. In the early 1970s, FDA management made an effort to remedy what it perceived to be barriers in the regulatory process,[11] and the changes that were implemented improved the FDA's standing in the scientific and medical communities. The increased supervision and guidelines relating to the nature of evidence required for approval have also made NDA approval more predictable. In Britain,

*During 1977 and early 1978, changes were occurring in the U.S. which would appear to narrow disparities still further. However, since full details of the comparable changes in Britain for the same period were not available, we consider here the 5-year period through December 31, 1976, for which complete data for both countries are available.

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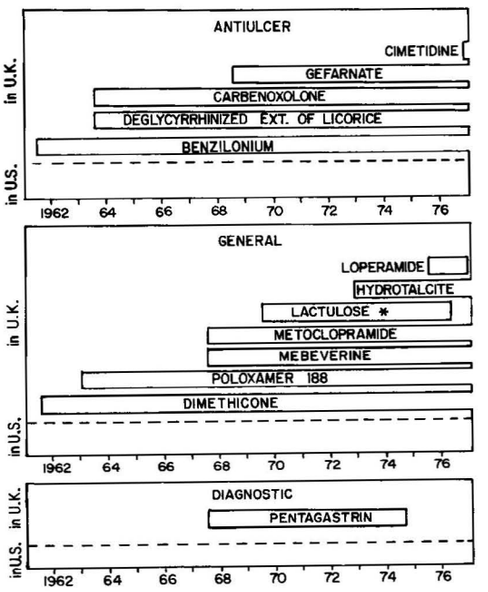


**Fig. 9.** Exclusive availability of gastrointestinal drugs. *This drug has been approved only for portocaval encephalopathy in the U.S.

regulatory requirements have increased rapidly in recent years and a more conservative trend is developing. This change may also have contributed to the convergence.

Another contributing factor may be that our initial studies, together with related studies and increased public awareness of this issue, have had an impact on the phenomenon being investigated. The demonstration of anachronisms in the drug approval process appears to accelerate their correction, as evidenced for example by FDA's handling of the propranolol NDAs for angina and hypertension and of beclomethasone for asthma. FDA's 1975 regulations regarding the acceptance of foreign clinical data and the new administrative procedures for prioritizing IND and NDA submissions according to their importance and degree of attention they are receiving from outside all suggest an awareness at FDA of the public interest in the drug approval process and the problem of drug lag.

The complexity of the risk-benefit decisions that must be made by a regulatory agency and the several types of influences that affect these decisions are well illustrated by the case of the β-blockers. It has been argued (see e.g., Reference 13) that the conservative attitude which FDA adopted toward β-blockers from the mid-1960s to date[6] was beneficial because it delayed by several years (and ultimately prevented) the marketing of practolol, along with several other post-propranolol β-blockers, preventing thereby cases of oculocutaneous and peritoneal toxicity[8] in the U.S. It should be noted, however, that the benefits of practolol to patients following an anterior myocardial infarction greatly outweigh the risks and that the proper use of practolol in postinfarction patients could save at least 10,000 lives per year in the U.S.[26]

Further implications of the delays in introduction of β-blockers to the U.S., including a 7-year setback in cardiovascular therapeutic research in the U.S., have recently been discussed in detail by Wardell.[21] The reasons for conservatism on the β-blockers in the U.S. are complex, as evidenced by the debate on this issue between FDA[4] and one of the industrial sponsors.[3] Substantial reaction against even the belated approval of propranolol for angina came from Congress (by which FDA was unfairly criticized for alleged hastiness in its approval[7, 14, 20]). The tortuous regulatory and scientific milieu that has surrounded the β-blockers in the U.S. is well illustrated in FDA's report on the subject.[6]

Other types of governmental and industrial considerations also influence the patterns of drug availability. In areas such as cancer chemotherapy and narcotic and narcotic-antagonist drug research, in which U.S. government agencies have positive mandates and funding to seek out improved therapies, the U.S. leads other countries in the range of drugs discovered and available. On the industrial side, foreign companies may be becoming more sophisticated in their penetration of the U.S. market (by licensing or by forming subsidiaries) and in satisfying U.S. regulatory standards, thereby contributing to the convergence of therapeutic patterns.

An important point to recognize in interpreting a comparison such as this study is that, since drug innovation and regulation are dynamic processes, a "snapshot" of the situation at one moment in time is less useful than a consideration that takes into account the longer evolu-

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ing a comparison such as this study is that, since drug innovation and regulation are dynamic processes, a "snapshot" of the situation at one moment in time is less useful than a consideration that takes into account the longer evolu-

tionary trends. While with some exceptions this study shows a narrowing of the therapeutic differences between the two countries, it also confirms that there have been large differences in the past, and it identifies the patterns and therapeutic areas on which attention should be focused in the future.

Differences in drug approval for specific *indications* are becoming increasingly important in comparative studies of this type. This is because, as stronger controls over drug utilization continue to gain in significance as determinants of therapeutic practice,[23] approval of specific indications becomes nearly as important as the fact of introduction. In Britain, except for those over promotion and excessive drug use, there are few controls; some drugs are approved first for use in hospitals only, which in practice restricts their use to specialists. In the U.S., control over utilization is becoming an important consideration as FDA seeks to increase the detail in the drug label and to constrain use to labeled indications and as the malpractice constraints of using a drug outside its labeling come to be more feared by physicians. Congress is seeking, as evidenced by the bills that have been introduced in the past few years culminating in the Drug Regulation Reform Act of 1978, to give FDA the power to constrain by legal means the power of physicians to prescribe drugs for purposes outside approved labeling. Where possible in our study, data were provided on important differences between approved indications for a drug in addition to information on its initial approval or introduction.

The ease with which gross disparities can be detected between countries suggests that much useful information could be gained by the continuous monitoring of international therapeutic differences. This would not be a difficult task, but it has received very little attention to date, even with respect to English-speaking countries alone. An example of the effect that differences in approval have on drug utilization in different countries is shown for antihypertensive drug usage in the paper by Petursson, Wardell, and Curran.[16] In future studies of this type, therefore, more information will be needed on the exact indications for which mutually available drugs have been approved.

International comparisons such as this should be only the beginning of attempts to chart therapeutic progress and to measure the impact of drugs and their regulation in therapeutic terms. We also need to know how to measure therapeutic impact, beneficial and adverse, that a new drug has on the whole community and—obviously further in the future—how to develop methods to assess the potential therapeutic impact of drugs that are prospective candidates for approval.

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Sigurdur R. Petursson, William M. Wardell, and John P. Curran

*Center for the Study of Drug Development*
*Department of Pharmacology and Toxicology*
*University of Rochester Medical Center*
*Rochester, New York 14642*

## INTRODUCTION

The therapy that a patient receives for a given medical condition can vary widely between countries, even those that have otherwise comparable standards of medical care.[1-3] There are several factors that determine international differences in the availability and use of drugs. The most obvious are the nature of the pharmaceutical industry that exists in each country, and the policy of the government drug regulatory agency that determines which drugs can be admitted to the market. Less obvious but equally important is the system of payment for drugs: third-party payment—particularly if the government is the payer—is a potentially powerful source of control over both drug availability and drug use.

During the 1960s and early 1970s, significant differences in drug availability arose between the U.S. and other western countries. This was largely due, particularly in the cardiovascular area, to the policy of the U.S. Food and Drug Administration (FDA), according to its own account.[4] In the field of hypertension, for example, no new drugs were approved in the U.S. for 10 years following the passage of the 1962 Drug Amendments, although, as will be shown, new drugs for hypertension continued to be approved and increasingly used abroad.

Several studies [5-13] have sought to characterize national levels and/or international differences in the prevalence of drug use for particular conditions, but none of the published data have dealt with international comparisons in the field of hypertension. The present study was therefore undertaken in order to examine the overall usage of antihypertensive drugs in the U.S., and to determine whether any differences could be detected in the level and patterns of drug treatment for hypertension among four countries: the U.S., the U.K., Australia, and New Zealand. The availability and use of antihypertensive drugs were com-

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† *Present address:* Presbyterian-University Hospital, Pittsburgh, Pennsylvania.

‡ Formerly with Pfizer, Inc., New York, N.Y. *Present address:* Wood Gundy, Inc. 100 Wall Street, New York, N.Y.



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pared using the available data on the total national consumption of every antihypertensive drug in each of the four countries.

## Methods

For the international comparison for the year 1972, data on total national drug sales to pharmacies were derived from the figures of Intercontinental Medical Statistics (IMS) in the four countries. These figures do not include hospital use, which would add approximately 10% to the total. For each dosage form of each drug, the total weight of drug (or, in the case of fixed-ratio combinations, the total number of dose units) sold in the given year was computed for each country. This amount was standardized to a per-1000-of-population basis in each country, using each nation's census data.[14-17]

For each drug, a dose was defined which, in the judgment of the authors, was a representative medium daily dose of that drug for hypertension. The

Table 1

Medium Defined Daily Dose of Hypotensive Drugs

| Drug | Defined Daily Dose (mg) |
|---|---|
| Reserpine | 0.25 |
| Rauwolfia serpentina alkaloids | 4.0 |
| Methoserpidine | 25.0 |
| Deserpidine | 0.5 |
| Rauwolfia whole root | 250.0 |
| Methyldopa | 1000.0 |
| Bethanidine | 60.0 |
| Guanethidine | 30.0 |
| Debrisoquine | 50.0 |
| Hydralazine | 150.0 |

determination of what constituted a medium dose was based on information derived from several sources: the medical literature; the respective countries' drug catalogues [18-22] and product labeling; and on the authors' experience. This medium dose assumption will henceforth be referred to as the Defined Daily Dose (DDD) for each drug. The DDDs we chose are shown in Table 1 for the most commonly used nondiuretic antihypertensives. They are in general similar to, but not always identical with, those listed in the Drug Dose Statistics published in 1975 by the Norsk Medisinaldepot,[23] which are closely based on a European International Working Group on Drug Utilization that was supported by the World Health Organization.

The next step in the calculation was to project the DDDs to a corresponding annual dose, and to divide the latter figure for each drug into its standardized annual consumption figure in order to obtain the number of DDDs of each drug consumed per 1000 persons over the year. This provides an approximate indication of the fraction of the population within each country receiving that particu-

lar drug. Finally, by summing the values for individual drugs, a figure was obtained for the total DDDs of all nondiuretic antihypertensives (NDAH) consumed annually per 1000 persons in each country. The percentage contribution of each drug to the total NDAH consumption in that country was also calculated.

For the longitudinal examination of all antihypertensive drug use in the U.S. from 1971 to 1976, the data computed by Curran from IMS figures were used,[24] and converted to daily doses per 1000 of population. Curran assumed slightly different values for the daily dose definitions, but his results agree very closely with the figures we obtained for the U.S. component of the international portion of this study.

Information on two types of antihypertensive drugs (plain diuretics and beta-adrenergic blocking agents) was not available in a form suitable for inclusion in the international portion of the present analysis. In the case of multi-use drugs such as the diuretics, even with prescription data from a survey such as (in the case of the U.S.) the National Drug and Therapeutic Index, it is not clear that one can obtain precise information on how much of each diuretic was used for hypertension, compared with its use for other indications, because the breakdowns vary widely depending on how the prescription-data questions are asked. For the longitudinal U.S. study, it has been assumed that 50% of all plain diuretics were used for hypertension. (This is in addition to those diuretics prescribed in fixed combination with other antihypertensive drugs, which are included in the figures for the respective nondiuretic antihypertensives, as described.) The data on the partitioning of diuretics among their various uses were not available to us for countries other than the U.S.

Data on the consumption of beta-blockers were also not available to us. In the case of the U.S., the beta-blockers were not approved for use as antihypertensives until 1976, so that only the latter portion of that last year should be greatly affected for the U.S. The effect this has on the interpretation of results is discussed later. Thus, our data deal primarily with those drugs that can be prescribed solely for hypertension.

Data on international availability of antihypertensive drugs were obtained as described previously.[1]

## Results

### *Patterns of Availability of New Antihypertensive Drugs in the U.S.A. and Britain, 1963–1976*

From Figure 1 and Table 2, it can be seen that no new antihypertensive drugs were admitted to the U.S. market for a 10-year period, i.e. from the admission of pargyline and methyldopa in 1963 to the admission of diazoxide in 1973. Abroad, however, antihypertensive drugs continued to appear throughout the 1960s and the 1970s. Table 2 compares the U.S. with Britain, by showing the approval dates of all new antihypertensive drugs from 1972 to 1976 in both countries and the differences in availability patterns that thus arose with time. It can be seen from Figure 1 that there arose a very marked preponderance of drugs available both earlier and exclusively for the treatment of hypertension in Britain. The difference at present is particularly marked in the case of beta-blocker drugs, of which eight are now available in Britain compared

with one in the U.S. However, even larger differences were present overall from the mid-1960s through the early 1970s.

*Increase in Consumption of Antihypertensive Drugs with Time in the U.S.*

There has been steady increase in the total consumption of both diuretic and nondiuretic antihypertensive drugs with time. This is shown in FIGURE 2, which displays the data available for the U.S. from 1971 to 1976. The total consumption (i.e. the sum of both diuretic and nondiuretitc antihypertensives), rose

TABLE 2

A SUMMARY OF NEW ANTIHYPERTENSIVE DRUG INTRODUCTIONS OR APPROVALS IN THE U.S. AND U.K. FROM 1963 THROUGH 1976 *

| Drugs | Date | | Lead (years) | |
|---|---|---|---|---|
| | U.K. | U.S. | U.K. | U.S. |
| Pargyline (*Eutonyl*) | 63 | 63 | 0 | 0 |
| Methyldopa (*Aldomet*) | 62 | 63 | 1 | |
| Bethanidine (*Esbatal*) | 63 | — | — | — |
| Guanoxan (*Envacar*) | 64 | — | — | — |
| Guanoclor (*Vatensol*) | 64 | — | — | — |
| Debrisoquin (*Declinax*) | 67 | — | — | — |
| Diazoxide (*Hyperstat*) | 72 | 1/73 | ½ | |
| Clonidine (*Catapres*) | 3/71 | 9/74 | 3½ | |
| Prazosin (*Minipres*) | 9/74 | 6/76 | 1¾ | |
| | *The Beta Blockers* | | | |
| Propranolol (*Inderal*) | 2/69 | 5/76 | 7 | |
| Practolol (*Eraldin*)† | 70 | — | — | — |
| Oxprenol (*Trasicor*) | 11/70 | — | — | — |
| Timolol (*Blocadren*) | 6/74 | — | — | — |
| Sotalol (*Beta-Cardone*) | 6/74 | — | — | — |
| Pindolol (*Visken*) | 10/74 | — | — | — |
| Acebutolol (*Sectral*) | 4/75 | — | — | — |
| Metoprolol (*Betaloc*) | 7/75 | — | — | — |

* These data are the best available to us as of March, 1977. In the case of multi-use drugs such as diazoxide and the beta blockers, the date shown is the date of approval for use as an antihypertensive if this is known to be different from the date of first introduction for any use.

† Practolol is now restricted to parenteral use in hospitals because of the toxicity that developed during chronic oral administration.

by 40%, from 22.6 DDD/1000 of population in 1971 to 31.5 in 1976. In the case of the nondiuretic antihypertensives, there was a shift from rauwolfia preparations, whose use declined, to other nondiuretic agents, whose increased use more than offset the decline in rauwolfia, so that the usage of NDAH rose by 28%, i.e. from 15.2 to 19.5 DDD/1000 from 1971 to 1976. More details of these "other" nondiuretic hypotensives are discussed in the next section and shown in FIGURE 3.

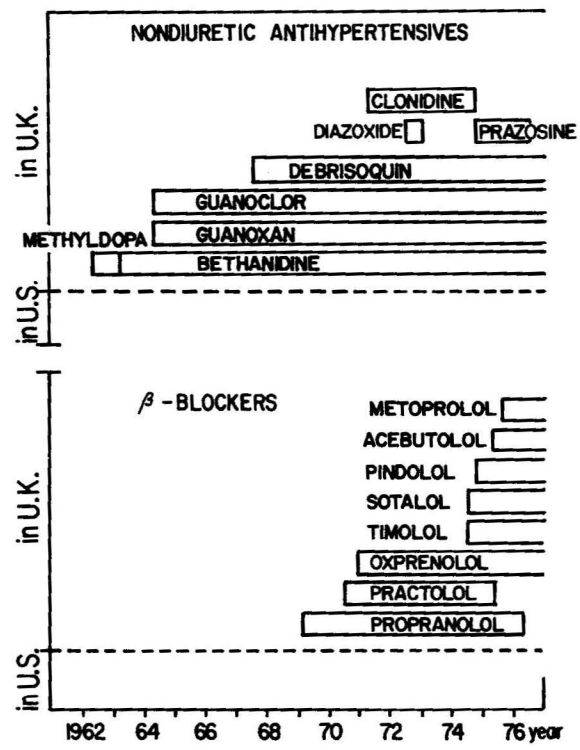


FIGURE 1. Graphical display of exclusive availability of antihypertensive drugs in the U.S. and U.K. (1962–1976), using data from TABLE 2. Two pharmacologic drug classes are shown: nondiuretic antihypertensives and beta blockers. The year is represented on the abscissa. In each pharmacologic class, a dashed horizontal line bisects the field. Those drugs that were exclusively available in the U.K. are plotted above this line, whereas those in the U.S. (of which there are none in this case) would be plotted below it. The horizontal bar representing each drug extends from the time it became exclusively available (or was approved for use in hypertension) until its exclusive availability ceased—which was usually because the drug was marketed in the other country. A vertical line drawn at any point in time allows one to see at a glance the *differences* between the range of drugs available in each country at that time. In both pharmacologic categories, there was an overwhelming preponderance of drugs exclusively available in the U.K.

### *International Differences in Total Nondiuretic Antihypertensive Consumption for the Year 1972*

Comparative data were available for all four countries for the year 1972, which marked the beginning of the HEW-sponsored National High Blood Pressure Education Program in the U.S.[25] The amounts of total NDAH consumption in each country (i.e., excluding diuretics alone and beta blockers) are shown in the upper portion of FIGURE 3. Among the four countries, the number of DDD/1000 ranged nearly twofold, from 11.7 in the U.K. to 20.7 in New Zealand. The U.S. occupied an intermediate position with 15.0

It is important to note, as already pointed out, that the beta blockers are not included here. As discussed later, this means that the British, New Zealand, and Australian antihypertensive consumption is underestimated here compared with the U.S. consumption.

### *Difference in Patterns in the Year 1972*

In addition to the marked differences in the total number of DDD/1000 between countries, there were large differences in the patterns of the drugs used. These differences are shown in the lower part of FIGURE 3, which shows the DDD/1000 for each of the three major drug groups that contributed over 95% of the total DDD/1000 in each country. These groups were rauwolfia alkaloids

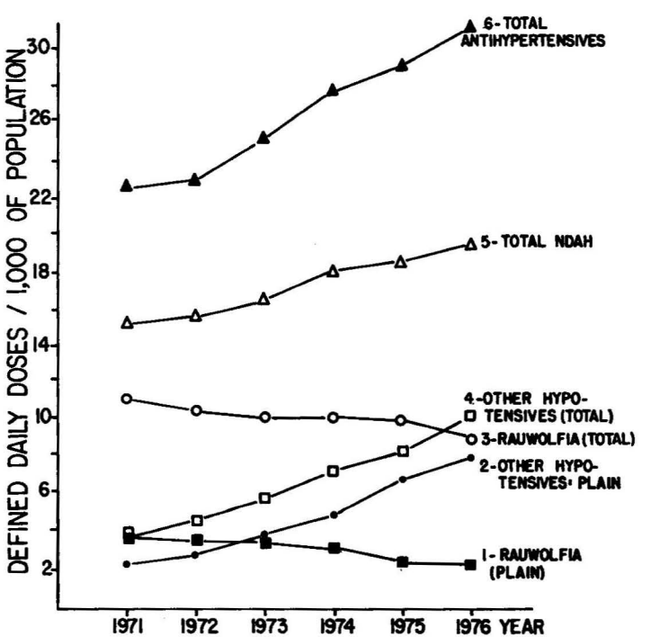


FIGURE 2. Consumption of antihypertensive drugs in the U.S. by year from 1971 through 1976 (abscissa), in terms of DDD per 1000 of population (ordinate). Line 1 shows plain rauwolfia, while line 3 shows total rauwolfia (i.e. including rauwolfia in fixed combination with other drugs, mainly diuretics). Line 2 shows the data for plain preparations of the other nondiuretic, non-beta-blocker hypotensives (which are mainly methyldopa and adrenergic neurone-blocking drugs), while line 4 shows the same data with the addition of fixed combinations of these drugs, again mainly with diuretics. Line 5 shows the total consumption of all nondiuretic, non-beta-blocker hypotensives, including fixed combinations; i.e., it is the sum of lines 3 and 4. Line 6 shows the total antihypertensive drug consumption, obtained by adding, to line 5, 50% of the total plain diuretic consumption.

(designated "R" in the lower portion of FIGURE 3), methyldopa ("M"), and adrenergic-neurone blocking drugs ("A").

One of the most striking differences in patterns is the heavy reliance on rauwolfia alkaloids in the U.S. On a per-capita basis, the consumption of rauwolfia alkaloids in the U.S. was more than four times the rate in the U.K., and even double the rate in Australia, despite the fact that the total NDAH use

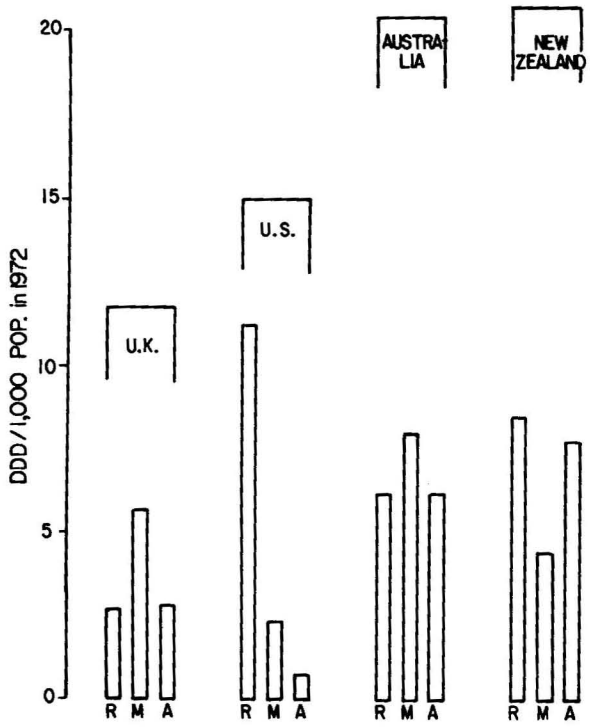


FIGURE 3. Consumption of defined daily doses per 1000 of population (ordinate) in the U.K., U.S., Australia, and New Zealand for the year 1972. The values shown are for all nondiuretic, non-beta-blocker antihypertensives including those in fixed combinations (mainly with diuretics) and thus correspond (within the limits described under 'methods') to line 5 ("Total NDAH") of FIGURE 2 in the case of the U.S.

The upper portion of the graph shows the total DDD/1000 for each respective country, while the lower portion shows the 3 major components making up the total: R=rauwolfia alkaloids; M=methyldopa; and A=adrenergic-neurone blocking drugs.

in Australia was considerably higher than in the U.S. On a percentage basis, rauwolfia alkaloids accounted for 75% of the total U.S. NDAH use, whereas in Britain, the fraction was 23%, i.e. less than a third of the U.S. fraction.

Conversely, the use of adrenergic-neurone blocking drugs was much higher in the other countries than in the U.S. On a per-capita basis, the use of these drugs was more than 10 times as great in New Zealand as in the U.S., while

the corresponding fractions of the total use were 38% and 5% respectively, representing nearly an eightfold difference.

Even within the class of adrenergic-neurone blocking drugs, some interesting differences appeared. In the U.S., the only member of this class of drugs is guanethidine, while in the other three countries, two additional drugs were available, bethanidine and debrisoquin, which together accounted for approximately one-third of the total adrenergic-neurone blocker usage in the three countries where they were available. Thus, comparing New Zealand with the U.S. on a DDD/1000 basis, New Zealand had more than six times the guanethidine consumption, plus an additional consumption (equivalent to nearly four times the U.S. guanethidine consumption) of adrenergic-neurone blocking drugs that were not available in the U.S.

The per-capita use of methyldopa also showed wide international differences, being lowest in the U.S. and highest (by a factor of 3.4 times) in Australia. In terms of the percentage of methyldopa in relation to total NDAH consumption, the U.S. had the lowest ratio (16%), while the U.K. had the highest (nearly 50%).

A further large difference could be seen in the use of fixed combination drugs, namely nondiuretic antihypertensives in fixed combinations with (for the most part) diuretics. In the case of rauwolfia alkaloids, for example, there were very wide variations in combination use, with the U.S. being a high user (74% of all rauwolfia DDDs used in the U.S. were in combination) and Australia having essentially no combinations at all. New Zealand and the U.K. were intermediate with, respectively, one-half and one-third of rauwolfia use being in fixed combinations.

## Discussion

The omission of the beta blockers in this study will have a differential effect on the estimates of antihypertensive drug consumption in the four countries, because the beta blockers were approved for use as antihypertensives much earlier outside the U.S. (1969 in the case of propranolol in the U.K., vs. 1976 in the U.S.). Furthermore, the actual use of beta blockers for hypertension became very widespread abroad before the drugs were approved in the U.S. For example, by 1975, 40 out of 100 patients attending an Australian clinic for severe hypertension were receiving a beta blocker, and this class of drugs was the third most commonly used after thiazides and methyldopa.[26] Therefore, the antihypertensive drug consumption estimates for the U.K., Australia and New Zealand will be underestimated here by the extent of beta-blocker consumption, compared to the U.S.

The comparatively high U.S. reliance on rauwolfia alkaloids in 1972 is consistent with, but not fully explained by, the relative lack of newer antihypertensive drugs available in the U.S. at that time. This situation probably accounts in part for the high use of the older drugs in the U.S., although it does not explain why the U.S. was relatively slow to switch from rauwolfia alkaloids to methyldopa, nor does it explain the low use of adrenergic-neurone blocking drugs in the U.S.

The relatively high exposure of the U.S. population to rauwolfia is of interest in another context—namely, that of the putative association between reserpine and breast cancer. In view of the initial reports in 1974 claiming that such an

association existed, and the subsequent evidence refuting the initial claims, there has understandably been some confusion about national policies with respect to this drug.[27] In the case of Norway, for example, the national response was to send a government warning to all physicians and pharmacies advising physicians to change their female patients from reserpine to alternative drugs whenever possible; sales of reserpine decreased by 60% over the next 3 months. The restriction of rauwolfia alkaloids would not be of major importance in a country that had already substantially replaced rauwolfia by alternative antihypertensive drugs, but if similar action had been taken in the U.S. it is obvious that this would have disrupted the major nondiuretic component of the nation's therapy for hypertension.

What actually happened in the U.S. was that the use of rauwolfia, which had been slowly declining up to 1974, then declined more rapidly from 1974 to 1975 (22% decline in plain rauwolfia prescriptions in a single year). Overall, from 1972 to 1976, there was a 20% decline in total rauwolfia use, but in the meantime there had been a threefold rise in the consumption of other drugs: consumption of the nondiuretic/non-beta-blocker class rose by 30% despite the fall in rauwolfia use. Thus, by 1976, the consumption of these nondiuretic antihypertensive drugs in the U.S. had risen to equal the Australian and New Zealand levels of 1972.

The relative position of the adrenergic-neurone blocking drugs is also intriguing. It is our impression that the way in which these drugs are viewed by physicians abroad (at least in New Zealand and the U.K.) differed substantially in 1972 (and still differs) from the way in which they are customarily viewed in the United States. In the U.S., they tend to be reserved for the treatment of severe hypertension, while in the other three countries they were used more readily and for lesser degrees of hypertension (this may have changed subsequently with the introduction of newer drugs such as the beta blockers).

Several reasons might account for the large overall differences shown between the U.S. and the other three countries. Physicians abroad at that time were probably more aggressive in treating hypertension, and it should be noted that even the method of measuring diastolic blood pressure is different. (In English-speaking countries outside the U.S., the level of diastolic blood pressure is customarily taken as the fourth Korotkoff sound [muffling] while in the U.S. it is taken as the fifth sound [disappearance]. This fact can produce up to 10 mm Hg difference in the measured diastolic blood pressure in the direction of underestimation in the U.S.[28]) This methodological difference alone could partially explain an increased readiness to treat hypertension abroad compared with the U.S. Finally, there is the role of drug promotion in increasing the usage of newer drugs, particularly at a time when there was more intense competition abroad due to the presence of more new drugs there. Such increased promotion, combined with the more favorable pharmacokinetics of bethanidine and debrisoquin (resulting in somewhat easier use by the physician and the patient) probably helped to create a different image for the adrenergic-neurone blocking class of drugs abroad.

It is clear, then, even from this initial study, that the analysis of national antihypertensive drug consumption data has a great deal of potential interest. The next step would be to stratify the total national consumption statistics using data that can reliably separate out the antihypertensive-use component of the two main multi-use drugs in this area, namely diuretics and beta blockers. With

such refinements, a very useful picture of national and international trends and differences in the treatment of hypertension could be obtained.

Finally, in the light of the large international differences that this study has already revealed, it would be of great interest to examine whether drug consumption data can be integrated with data on the incidence and severity of hypertension, and on the outcome of the disease. Considering that the now-classic Veterans Administration studies were performed with at least one drug (reserpine) whose use is rapidly declining, it now becomes important to determine whether the continuing advances in pharmacologic therapy for hypertension are changing the outcome of this disease.

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# Postmarketing Surveillance of New Drugs: I. Review of Objectives and Methodology

WILLIAM M. WARDELL, M.D., Ph.D., MICHAEL C. TSIANCO, M.A., M.S., SADANAND N. ANAVEKAR, M.D., Ph.D.,* and HENRY T. DAVIS, Ph.D. Rochester, N.Y.

PREMARKETING clinical evaluation of a new drug, even if thorough and well conducted, still leaves some important questions about that drug unanswered. Studies carried out during the premarketing phase are restricted to limited numbers of patients and are usually of short duration. Conclusions derived from such studies may therefore be of limited generalizability to the use of the drug in actual practice.

There have been numerous discussions of the need to improve postmarketing surveillance of new drugs.[1-8] Proponents believe that the benefits which might result from such improvements, properly applied, could include facilitation of the drug development process and increased protection of patients. Others have concerns that, if postmarketing surveillance were introduced in the form of a legislative or regulatory requirement, however well intended, its effect could inevitably be to slow therapeutic progress by adding another regulated step to the already cumbersome process of drug development and approval.

Three drug bills were introduced in Congress in 1977[1-3] which provided that the FDA Commissioner could issue limited or conditional approval of new drugs before marketing or before final approval of a new drug application (NDA) and could set conditions for the use and distribution of a drug. One bill[2] combined this feature with the formal addition of a postmarketing phase (Phase IV) to the three existing premarketing phases of regulated clinical drug investigation. A recently introduced consolidating bill, the Drug Regulation Reform Act of 1978,[4] retains similar provisions. FDA Commissioner Donald Kennedy has stated that "One goal [of the proposed revisions of the present drug law] is to enable FDA to approve useful new drugs more quickly, provided we also can remove them quickly if necessary. If we are able to meet this goal a dependable post-approval drug monitoring system is essential."[9]

Although the FDA has already used its existing powers to require formal post-

From the Center for the Study of Drug Development, Department of Pharmacology & Toxicology and the Department of Biostatistics, University of Rochester Medical Center, Rochester, N.Y. 14642. This paper is based on a study performed for the Experimental Technology Incentives Program (ETIP), National Bureau of Standards. A preliminary report was published by ETIP as NBS-GCR-ETIP-76-35. This work represents the views of the authors and does not necessarily reflect the views of the National Bureau of Standards.

* Current address: Clinical Pharmacology and Therapeutics Unit, Department of Medicine, Austin Hospital, Heidelberg, Victoria 3084, Australia.



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essential."[9]

Although the FDA has already used its existing powers to require formal post-

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marketing studies on at least six drugs from 1969 through 1976, there has been remarkably little systematic study of how such a system could be implemented in a way that is both scientifically sound and practically feasible.

The aims of the present study were to use the information that can be currently obtained on existing studies to (1) identify examples of postmarketing surveillance (PMS) that have already been carried out; (2) review the methodology available for PMS in relation to the aims of such studies, using the actual examples on which data could be obtained; (3) analyze these examples in technical terms, particularly experimental design and statistical power; and (4) examine their costs and benefits where sufficient data exist.

The case examples analyzed here are not the products of any comprehensive "system" of postmarketing surveillance; no such system yet exists in any country. The examples represent studies that have been conducted because of special perceived problems or needs which have arisen in relation to individual new drugs. A careful study of examples such as the ones compiled here will clarify the design requirements for an effective system or systems of PMS.

## Objectives of Postmarketing Surveillance

There are two primary objectives of PMS. The first is to study a drug's efficacy and toxicity under conditions approaching its actual clinical use in order to identify particular conditions of benefit or hazard. These conditions will include, among other factors, disease and compliance (adherence) variables.

The second major objective is to evaluate the overall impact—both potential and actual—of a drug on the conditions for which it is prescribed. Ideally, both short-term and long-term impact should be measured and both beneficial and adverse impacts identified.

## Designs for Postmarketing Surveillance Studies

While the experimental designs available for PMS studies are broadly similar to the methods used for any drug study, the diversity and complexity of the objectives described above make it obvious that no one design or study will satisfy all the goals of PMS. Furthermore, there are several important differences in pattern, in emphasis and in the situation in which PMS studies are performed, from the methods used for the first three phases of clinical investigation.[5] These differences include (a) the larger patient population available; (b) the economic attractiveness of uncontrolled or historically controlled designs; (c) the tendency to favor nonrandom assignment of subjects to treatment groups; (d) the lack of control over subgroups within which data are collected; (e) the long-term or open-ended nature of such studies; and (f) the fact that they have not to date been subject to substantial formal regulation.

There are two fundamental types of PMS: descriptive and analytic. The descriptive approach seeks to describe the occurrence of events related to drug toxicity and efficacy in various populations, while the analytic approach seeks to determine associations or causal connections between such observed effects and particular drugs, and to measure the size of such effects.

Descriptive studies, while scientifically the less rigorous, occupy an important place in PMS designs. One reason is that they are a fertile source of hypotheses that will become starting points for analytic studies. (In its most elemental form, the raw reports of a spontaneous adverse reaction reporting system and the



evaluate the overall impact—both potential and actual—of a drug on the conditions for which it is prescribed. Ideally, analytic studies. (In its most elemental form, the raw reports of a spontaneous adverse reaction reporting system and the

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"Letters to the Editor" columns of medical journals in which newly observed drug actions are reported are examples of descriptive types of PMS.) Also, PMS studies may have to be carried out on large numbers of patients over a relatively long period of time (for example, if the objective is to detect low-incidence events). In such cases, the economics of the studies become a major limiting factor, along with bias and statistical power. This is one of the main reasons for the attractiveness of nonexperimental, particularly descriptive, designs for PMS studies as compared with formal experimental designs.

Many of the current proposals for PMS systems are for the descriptive type. If one wishes to discover any new or unexpected side effects of a drug, then a descriptive study in which data on many variables are collected on a large number of patients would, for a given cost outlay, have a better chance of detecting such side effects than would a tightly designed analytical study. On the other hand, as will be discussed later, establishing a causal role is usually difficult—if not impossible—without an appropriate formal experimental design.

In the case of an analytic study, one would like to be able to conclude as a result, with a high degree of confidence, that the drug under investigation either does or does not cause the suspected event (toxic or beneficial). In achieving this goal, there is a fundamental difference between formal experimental and nonexperimental analytic approaches.

Experimental studies, in which the investigator assigns the treatments according to objective procedures such as randomization or minimization,[10] are capable of yielding definitive answers. On the other hand, nonexperimental studies such as surveys (cohort and case-control studies) can only show whether or not there is an association between the drug and the putative effects; they cannot prove a cause–effect relationship.[11] This fundamental defect of the nonexperimental designs arises from the potential for bias inherent in the method of treatment assignment.

The characteristics of controlled experiments, cohort studies, and case-control studies will now be considered in detail. In the context of PMS, each available design method has advantages and disadvantages for particular needs and situations; no single method can be expected to answer all the questions that may be posed.

### *Controlled Experiments*

These involve two or more treatment groups, and the controls may be another active drug, placebo, or both. Only in the controlled experiment can objective treatment assignment procedures such as randomization or minimization be used to protect against bias. It is also possible to introduce blinding of treatments and individuals and to balance important ancillary variables (age, sex, obesity, etc.) within treatments to provide more protection against bias. Because of the prospective nature of the controlled experiment, it is possible to ensure, or at least measure, compliance with the treatment regimen.

Patient recruitment is more difficult for a controlled experiment than for the other designs and dropouts are frequently a problem. There may be ethical problems associated with treatment assignment.

Controlled experiments allow one to estimate the incidence of side effects in all treatment groups; furthermore, as will be discussed later, meaningful power statements can be made. They are the most expensive of the three designs discussed here. However, with a few exceptions, they provide evidence which is gen-



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most expensive of the three designs discussed here. However, with a few exceptions, they provide evidence which is gen-

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erally the most acceptable to the scientific community.

*Cohort Surveys*

These may be either controlled or uncontrolled. If they are uncontrolled and one wishes to use them for analytic purposes, then data on comparable populations (such as historical controls) must be available. Without impeccable data on comparable populations, the lower cost of an uncontrolled cohort survey always tends, if used for analytic purposes, to be offset by questions about its validity. Nevertheless, such a study can still have great value for descriptive purposes.

*Controlled Cohort Surveys*

Depending on when the study is performed in relation to the formation of the cohort, these studies may be prospective or retrospective* (or, in Feinstein's terminology,[12] "prolective" or "retrolective").

As previously indicated, a nonrandom, nonobjective method of treatment assignment (usually medical judgment or patient preference) is used in cohort surveys. This is where the possibility for bias and the resultant weakening of the study's conclusions arise.

Just as in controlled experiments, it is possible to "block" individuals with respect to important ancillary variables within treatments to reduce bias. However, it is not generally practical to use blinding techniques, so that observer and patient bias become additional sources of error.

In a prospective cohort survey, as in a controlled experiment, it is possible to monitor and maintain patient compliance with the treatment regimen. This is usually impossible for the retrospective type.

Although retrospective cohort surveys are rare, they may become more common with the growth of medical record linkage systems. The recruitment of patients is easier in a prospective cohort survey than in a controlled experiment, but recruitment and dropouts leading to bias and missing data are still problems. In a retrospective cohort survey, the "recruitment bias" problem attains a new dimension because the population from which it is possible to draw cohorts is only a subpopulation of the population about which inferences are desired.

From cohort surveys, it is possible to estimate the incidence of side effects in all treatment groups and to make meaningful power statements, just as in an experiment. The ethical problems involved in cohort surveys are much less than in experiments but nevertheless still exist.

In general, then, the evidence obtained from cohort surveys is less scientifically secure than that obtained in controlled experiments, but it is more generally accepted than that available from case-control surveys. In terms of cost, cohort surveys are cheaper than experiments but more expensive than case-control surveys; among cohort surveys, prospective ones are more expensive than retrospective ones.[11]

*Case-Control Surveys*

In the context of postmarketing surveillance, this method begins with putative drug effects and uses data on individuals free of the suspected side effects as controls. The frequency of drug exposure in the two groups is then determined and compared. Since treatments were not assigned randomly, and for several other reasons to be discussed, bias is a major source of concern.[13,14]

* When a study is loosely described as "retrospective," it is not immediately clear whether a cohort or case-control survey is being referred to. As a result, all the weaknesses of case-controlled studies may be mistakenly attributed to retrospective cohort studies.



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To protect against bias, attempts are made to match control patients with cases in terms of important ancillary variables. Matching is comparable in intent to the blocking described in the previous designs. However, since the information used in matching is obtained retrospectively and may not be as complete or accurate as that used in the other types of studies, the protection it confers against bias may not be as great as in controlled experiments and prospective cohort surveys. Blinding is also much more difficult in a case-control study than in either an experimental or cohort study.

Unlike experiments and prospective cohort surveys (but like retrospective cohort surveys), case-control surveys do not permit strict attention to treatment compliance. In addition, case-control studies generally utilize retrospective data collection methods which usually rely on patients' recollections and existing patient records (often nonstandardized or incomplete) which were not collected with the objectives of the study in mind. These methods may increase bias.[6,13]

Because of the logical structure of the case-control approach, the conventional questions of patient recruitment and dropout do not arise. Instead, they are replaced by much more formidable problems both in the methods for selecting the case and the control groups, and also in the retrospective determination of treatment exposure. Furthermore, one often does not know the relationship that the subpopulations from which case and control groups were selected bear to the population of interest (i.e., all individuals who do or will receive the treatment). Unlike experiments and cohort surveys, case-control surveys do not enable one to estimate the incidence of side effects within treatment groups. Meaningful power statements are at best difficult to make.

Bias tends to be a greater problem in case-control studies than in (nonexperimental) cohort studies for the reasons already described. Evidence from case-control surveys is nevertheless the cheapest and simplest to obtain of all the designs considered here and is a fertile source of hypotheses for further evaluation.

As an illustration of the operational differences between the above main designs as they apply to postmarketing surveillance, we may consider the PMS of oral contraceptives (OCs). To perform an experiment would require that the study be limited to women who would accept, and were medically suitable for, random assignment to the OC in question or to the other selected control contraceptive methods. (This would probably severely limit the study population from the outset.) Treatments would then be assigned and all groups would be followed according to a defined protocol.

To perform a prospective cohort survey,[15] women seeking contraception would be medically advised and allowed to choose the contraceptive method best suited to their medical and social needs. The various treatment groups thus chosen would be followed according to a protocol similar to the experimental study. The main problem would be bias in the allocation of treatments, so that the OC group would tend to differ at the outset from the other groups. (In a study of this type analyzed by two of the present authors, the between-group disparity was so large that a special team had to be recruited to analyze the results.)

In a retrospective cohort survey, a retrospectively defined study group of women would be broken into treatment cohorts on the basis of their retrospective determined contraceptive history. The results would then be analyzed as for the prospective cohort survey.

To perform a case-control study,[15,16] women who have experienced a putative adverse reaction (e.g., a thromboembolic



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To perform a case-control study,[15,16] women who have experienced a putative adverse reaction (e.g., a thromboembolic

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event) would be matched in some way with women who have not, and the histories of all women would be searched for exposure to OCs.

### *Spontaneous Voluntary Reporting Schemes*

In terms of experimental design, spontaneous reporting schemes are surveys that could, in principle, be treated in a cohort or a case-control manner, or as simple descriptive studies. The nature of the objectives, together with other details of how the data are collected and analyzed, determines which type of design is actually involved.

Spontaneous reporting schemes (in common with almost all postmarketing surveillance activity to date) have been used primarily for studying adverse drug reactions rather than for obtaining information on efficacy. One primary aim of these schemes is to act as "early warning" systems.[17] However (with some notable exceptions), it is not until a reaction has already been identified and putatively attributed to a particular drug that it shows up reliably in formal spontaneous reporting schemes. For example, the recent discovery of the oculocutaneous side effects of the cardioselective beta-blocking drug practolol were essentially missed by the formal "early warning" yellow card spontaneous reporting system in Britain, until they were first reported in the correspondence columns of medical journals. On the other hand, informal spontaneous reporting such as "Letters to the Editors," of medical journals are a rich source of spontaneous reports. Once a possible reaction has been thus described, it tends to be heavily emphasized in the more formal spontaneous reporting systems ("trigger effect"). The real value of spontaneous reporting systems in the early detection of hitherto unknown adverse reactions is not yet fully determined. Nevertheless (subject to the caveats to be described), spontaneous reporting schemes are potentially useful for keeping track of the patterns of reactions associated with particular drugs and for comparing the reaction patterns of related members of a particular therapeutic class.

A major problem that limits the usefulness of spontaneous reporting systems is underreporting and selective reporting.[18] Underreporting will lead to the false conclusion that a real risk is absent, while the selected reporting of suspected risks may give a false impression of a risk that does not exist. The collection of voluntary reports, even when supported by a denominator data on drug consumption, needs to be followed up by more formal epidemiological techniques that enable reliable estimates to be made of the incidence of reported effects.

Another major problem of spontaneous reporting systems is in establishing cause–effect relationships. While this problem is common to all the nonexperimental designs, it is particularly marked in the case of spontaneous reporting.

## Statistical Power

A key factor in the design and evaluation of postmarketing surveillance studies is the question of statistical power. Given the sample sizes actually involved and ignoring for the moment the problem of bias, what sized difference between treatment and control groups has a reasonable chance of being detected? Conversely, given the magnitude of a clinically (or epidemiologically) important difference, what sample sizes are needed?

The answers to these questions of statistical power determine the costs of the studies and in turn the cost–benefit analysis of the whole PMS exercise. Because of its key importance, a brief discussion of statistical power in general and of its particular application to PMS will be given here.



porting systems in the early detection of hitherto unknown adverse reactions is not yet fully determined. Nevertheless (subject to the caveats to be described), spon- cause of its key importance, a brief discussion of statistical power in general and of its particular application to PMS will be given here.

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The power of a statistical test is the probability that it will indicate a statistically significant difference (in this case, between the effects of two or more treatments) when a real difference indeed exists. The power of a given test depends upon the significance ($\alpha$) of the test, the precision of the sample results, and the "effect size."

In general, the significance level is an upper bound on the probability of rejecting a true null hypothesis. Other things being equal, a reduction in significance level results in a reduction of power; therefore, one way of increasing power is to raise the $\alpha$ level of the test, that is, to increase the Type I error.

An increase in precision results in an increase in power. As Jacob Cohen describes it[19]:

> "The reliability (or precision) of a sample value is the closeness with which it can be expected to approximate the relevant population value. . . . Depending upon the statistic in question, and the specific statistical model on which the test is based, reliability may or may not be directly dependent upon the unit of measurement, the population value, and the shape of the population distribution. However, it is always dependent upon the size of the sample."

Other things being equal, an increase in sample size results in greater precision which in turn results in greater power. A well-planned experiment will use an experimental design that eliminates extraneous sources of variability, thereby increasing precision and thus power.

"Effect size" refers to how far from the truth the null hypothesis really is or, in PMS terms, the difference in incidence rates of putative drug effects between the test and the control treatment groups. All other things being equal, the larger the effect size the greater will be the power of a test. This means, for example, that on the null hypothesis (an incidence rate is the same in two treatment groups) our chances of rejecting this hypothesis based on sample data are greater if the incidence rates are 0.1 and 0.3 rather than 0.1 and 0.2; the difference between population incidence rates in the two groups is the "effect size."

In order both to plan and to evaluate a study, one needs some estimate of how large an effect size must be to become scientifically or clinically important. As Fleiss points out, "Given no information [about the size of an important difference], the investigator has no basis for designing his study intelligently, and would be hard put to justify designing it at all."[20] This statement derives from the nature of the relationships between power and effect size and between power and sample size.

A further important point about incidence rates is that one needs to know, in addition to the effect size, where the two rates lie on the interval from 0 to 1. That is, is the effect common or rare?

The dynamics of the factors influencing power are illustrated in Tables I, II, and III, which show the sample sizes required in the types of situations encountered in PMS studies. The columns of each table show how sample size increases with increasing power. Although the difference between population incidence rates in each of the first three columns in all tables is 1 in 10,000, the sample size needed to achieve a fixed power increases as the magnitude of the rates increases. The first, fourth, and fifth columns show that as the incidence rates (and the difference between them) increase by an order of magnitude, the sample size needed to achieve a given power decreases by approximately an order of magnitude. (The sample sizes indicated are for one treatment group; a two-treatment study, such as drug vs. placebo, would require twice the number of patients shown here.) These sample sizes pertain to both controlled experi-



the effect size the greater will be the power of a test. This means, for example, that on the null hypothesis (an incidence rate is the same in two treatment groups) two-treatment study, such as drug vs. placebo, would require twice the number of patients shown here.) These sample sizes pertain to both controlled experi-

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**TABLE I**

**Sample Size Needed in Each Treatment Group to Achieve the Indicated Power, $\alpha = 0.05$***

| Desired power | No. with side effect per 10,000 in treatment vs. control populations | | | | |
|---|---|---|---|---|---|
| | 1 & 2 | 10 & 11 | 100 & 101 | 10 & 20 | 100 & 200 |
| 0.5 | 112,000 | 805,000 | 7,640,000 | 11,200 | 1,100 |
| 0.7 | 180,000 | 1,290,000 | 12,300,000 | 18,000 | 1,770 |
| 0.9 | 306,000 | 2,200,000 | 20,900,000 | 30,600 | 3,020 |
| 0.99 | 535,000 | 3,850,000 | 36,600,000 | 53,500 | 5,280 |

* Sample size is indicated to three significant digits. For a two-treatment study, the total number of patients is double that shown in the table. The calculations employ angular transformation and involve a two-sided test of the equality of incidence rates.

**TABLE II**

**Sample Size Needed in Each Treatment Group to Achieve the Indicated Power, $\alpha = 0.10$***

| Desired power | No. with side effect per 10,000 in treatment vs. control populations | | | | |
|---|---|---|---|---|---|
| | 1 & 2 | 10 & 11 | 100 & 101 | 10 & 20 | 100 & 200 |
| 0.5 | 78,000 | 567,000 | 5,380,000 | 7,870 | 777 |
| 0.7 | 137,000 | 986,000 | 9,360,000 | 13,700 | 1,350 |
| 0.9 | 250,000 | 1,800,000 | 17,000,000 | 24,900 | 2,460 |
| 0.99 | 460,000 | 3,310,000 | 31,400,000 | 45,900 | 4,530 |

* Sample size is indicated to three significant digits. For a two-treatment study, the total number of patients is double that shown in the table. The calculations employ angular transformation and involve a two-sided test of the equality of incidence rates.

**TABLE III**

**Sample Size Needed in Each Treatment Group to Achieve the Indicated Power, $\alpha = 0.20$***

| Desired power | No. with side effect per 10,000 in treatment vs. control populations | | | | |
|---|---|---|---|---|---|
| | 1 & 2 | 10 & 11 | 100 & 101 | 10 & 20 | 100 & 200 |
| 0.5 | 47,800 | 344,000 | 3,260,000 | 4,770 | 471 |
| 0.7 | 95,000 | 683,000 | 6,490,000 | 9,490 | 936 |
| 0.9 | 191,000 | 1,380,000 | 13,100,000 | 19,100 | 1,890 |
| 0.99 | 379,000 | 2,730,000 | 25,900,000 | 37,900 | 3,740 |

* Sample size is indicated to three significant digits. For a two-treatment study, the total number of patients is double that shown in the table. The calcualtions employ angular transformation and involved a two-sided test of the equality of incidence rates.



* Sample size is indicated to three significant digits. For a two-treatment study, the total number of patients is double that shown in the table. The calcualtions employ angular transformation and involved a two-sided test of the equality of incidence rates.

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ments and controlled cohort surveys; in the latter design, however, the bias problems have to be ignored. It is important to note that if significant bias related to treatment assignments is present, it may be necessary to employ more sophisticated statistical analytic procedures to correct for this bias. However, if these procedures are used when such bias is not present, then a loss of power will result.

The magnitudes of the sample sizes shown in Tables I, II, and III clearly illustrate the compromise that must be made between the significance ($\alpha$) level, statistical power, and sample sizes (costs). The effect of significance level on the sample size needed to achieve a given power is seen by comparing Tables I, II, and III. In the context of PMS, because of the very large sample sizes and costs that will be required to detect uncommon drug-related events, there may be a tendency to increase the $\alpha$ level and thus increase the risk of making erroneous associations between drug and effect (Type I error).

Thus, in spite of all their weaknesses, it is easy to see why case-control studies have some appeal in the study of rare side effects; case-control studies sample a larger fraction of cases for the same outlay than do the other types of designs. There is a further attraction involving statistical power. If, in the population, the incidence of a medical event that could be a drug side effect is lower than the frequency of drug administration (more precisely, if the probability of being administered the drug is closer to 0.5 than is the probability of experiencing the side effect), then, all other things being equal, the chi-square test on data from a case-control study is more powerful than the chi-square test of a controlled cohort survey.[20] (It should be noted, however, that this is a test of the *ratio* of the two incidence rates and not their difference.)

In one of the examples to be discussed in part II of this paper, the design possibilities of historical controls are explored by comparing studies involving controls with those not involving controls. If the concurrent control group could be replaced by historical controls and if bias were not a serious problem, then power could be increased by having a larger (double-sized) treatment group for almost the same amount of effort. However, what one gains in design efficiency is offset by the loss of control over bias.

Apart from the potentialities and limitations of the different designs already discussed, there are two further points that should be noted about PMS studies in general[6]:

1. Even a highly sophisticated PMS system would not be suitable for assessing the occurrence of extremely rare reactions or responses. No system yet known or likely to be developed can fully meet this need. We must recognize that below some level of individual risk or hazard, no protection beyond general, careful observation and quality control is possible.

2. Similarly, a single system—even if highly developed—could not be applied to investigate all responses to all reactions in the wide variety of settings under which PMS studies need to be conducted. Drugs used in rare diseases or applied to a relatively small population of patients may not be amenable to adequate study by a general system. (In any case such therapeutic agents do not, individually at least, constitute the potential hazard to public health provided by more widely prescribed medications.) Clearly, each method has its own advantages and disadvantages and no single method can be relied upon to answer all questions that may be posed. Each method answers a particular need, and difficulties can result when attempts are made to apply specific methods to problems



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outside their domain of appropriate application.

In the second part of this paper we seek, by means of a case-study method, to add to the very meager stock of information that currently exists about the methodology of postmarketing surveillance.

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