You no doubt also will agree that the aminopyrine derivatives such as Butazolidin and the steroids like Prednisone are too risky for long term use.

Yet, until now, aspirin, aminopyrine derivatives, and steroids have been the only major agents available for relieving pain and reducing disability in a whole host of rheumatic problems.

Now, today, 'Indocin'—a new non-steroidal anti-inflammatory agent which approaches the potency of the steroids—equals or surpasses the effectiveness of Butazolidin—but which in therapeutic doses has a safety index comparable to aspirin is

Available to relieve pain.

Reduce fever tendencies and swelling and increase joint mobility in patients with rhenmatic disorders.

For the physician who is presently prescribing Darvon.

Doctor, you no doubt agree that pain and disability are the most common complaints of patients with rheumatoid problems.

Would not a drug that can control long term pain in such patients yet in therapeutic doses be as safe as aspirin fill a real need?

'Indocin'—a new non-steroidal anti-inflammatory agent has a potency equal to or greater than Butazolidin—which as you know is an aminopyrine-like synthetic.

'Indocin' usually controls acute arthritic pain within one to two hours.

However, 'Indocin' is more than just an ordinary analgesic like aspirin or Darvon because 'Indocin' has anti-inflammatory activity which is almost equal to full dose steroids.

For the conservative therapeutic nihilist.

Doctor, it is true that no patient ever dies from chronic rheumatoid arthritis—but they do become cripples who live a very limited life.

The burden of crippling disability imposed by chronic rheumatoid arthritis can now be lifted in three out of four patients on therapy with 'Indocin'.

No matter what approach you use—no matter what story you tell—make certain that when you leave the office the physician agrees that

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling—

When the muscles around an inflamed joint are in spasm causing a limitation in motion—

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain muscoskeletal aches and stiffness—

For short term use in acute conditions or long term use in chronic diseases—

'Indocin' will afford relief to three out of four patients effectively—with an extended margin of safety—with fewer tablets—at less cost—with less dosage adjustment—and therefore fewer problems for both the physician and his patient than any other currently available product.

Go get it!!!

BULLETIN NO. 87, JULY 20, 1965

To: Mr. Gordon R. Klodt.
From: H. Glassner.
Subject: 'Indocin' Profit Plan Objectives.

Surely you jest. The 'Indocin' Profit Plan Objectives for the Western District have just arrived. Your ouija board has a definite short circuit. The figures you forwarded are so ridiculously low that they are a rank insult to the hottest, sellingest district in the country. Only because these figures will appear on the official R–300 and R–317 reports beginning with July, 1965 are we even bothering to forward them to our associates since we intend to smash them.

We realize these dollar objectives were calculated by determining the percentage of sales in each territory of 'Decadron' Tablets and Injection, 'Decagesic', 'Benemid' and 'ColBenemid'. Apparently, the same percentages were then used in determining the percentages of the total objective for each territory on 'Indocin'. Apparently, you next built the territory objectives into the Field Manager Group objective and then the district total. Yet even though your approach

was rational, I'll Bet You the Price of a Bottle of Your Favorite Booze that the Western District Beats this Objective by at Least 50% This Year.

Heck, Gordon, 'Indocin' is the hottest product we've had come down the pike in many a moon. Our guys are primed at fever pitch. Competition is running scared. Results on recalls look great.

The only questions we are getting regularly are easily handled such as:

Does 'Indocin' affect prothrombin levels? The answer, of course, is "No."

Does 'Indocin' affect glucose tolerance? The answer, again, of course is "No." 'Indocin' can be safely used on the diabetic patient.

In fact, our guys are using a real expanded claim for 'Indocin' on inflammation. They are consistently telling their doctors that—

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling—

When the muscles around an inflamed joint are in spasm causing a limitation in motion—

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain musculoskeletal aches and stiffness—

For short-term use in acute conditions, or long-term use in chronic conditions—

'Indocin' will afford relief to 3 out of 4 patients effectively—

With an extended margin of safety—

Probably with fewer tablets—

Therefore, at less cost—

With less dosage adjustment—

And, therefore, fewer problems for both the physician and his patient than any other currently available product.

For these reasons—we intend to really roll up the 'Indocin' bonus credit points this year. We'll be laughing at you when we make our year's objective by October 30.

BULLETIN No. 88, JULY 21, 1965

To: All Western District Sales Associates.
From: H. Glassner.
Subject: 'Indocin.'

Jim Blake is kind of new. He is a pharmacist, so he has developed a very healthy respect for what drugs will and won't do. I suppose he just doesn't know any better than to sit down and prepare a detail that puts side effects in their proper perspective. Here is how he is handling the side effects on 'Indocin'.

"Chemically, 'Indocin' is indomethacin. The only similarity in structure between 'Indocin' and steroids or phenylbutazones is that all three are organic compounds. After that, the similarity ceases.

The ability of both the steroids and phenylbutazones to relieve inflammation is unquestionable. However, both of these agents cause undesirable—and, in the case of phenylbutazones—even hazardous side effects. So, doctor let's examine the relative lack of side effects of 'Indocin'.

In six out of ten patients on 'Indocin', you need anticipate no adverse effects whatsoever.

In two out of three of these ten patients, some bothersome effects might occur. Bothersome is probably as severe an adjective as we can use to describe these effects because in most patients they are tolerable, and transient.

Reports of changes in the white blood count of patients on therapy with 'Indocin' have been exteremely rare. In most cases, it has been impossible to implicate 'Indocin' as the causative agent. Unlike phenylbutazone, patients on therapy with 'Indocin' do not require weekly or bi-weekly blood counts.

Unlike steroids, therapy with 'Indocin' does not depress adrenal function, decrease resistance to infections, or present withdrawal problems.

The percentage of patients experiencing side effects, which are listed in this chart, needs some explanation. Originally, our studies on 'Indocin' were done with tablets. For some unknown reason, the tablets did not disintegrate properly and absorption was erratic. Now, commercially, 'Indocin' is being marketed as a capsule. In capsule form, 'Indocin' has not caused as high a percentage of even these minor reactions. These charts, however, do include the side effects experienced with the earlier tablets which are not even available on the market. Therefore, the incidence of adverse reactions which you

probably will experience in your patients will be somewhat lower than these figures indicated here.

You will note that gastrointestinal disorders head the list. This irritating effect can be markedly reduced by taking 'Indocin' after meals.

Headaches are next in frequency. These headaches are mild and are readily relieved by caffiene. Usually a cup of coffee does the job.

Lightheadedness and dizziness occurs occasionally with 'Indocin' as with almost any other medication. For the most part, these effects are very mild and very transient.

Diarrhea accounts for less than 2% of all reactions.

You will also note that the incidence of peptic ulcer is less than 1.5%. Since it is estimated that 7 to 7.5% of all arthritic patients have ulcers—Probably Because of the Large Amounts of Aspirin and Steroid Which These Patients Have To Take Over Long Periods of Time—It is hard to construe this effect of 'indocin' as being a true side effect.

In summary, doctor, six out of ten patients on 'Indocin' probably will experience no adverse reaction.

Two out of three of these ten patients may experience some mild adverse effects which are transient and tolerable.

And, only one out of ten of these patients will probably experience side effects severe enough to warrant a reduction of dosage.

On the basis of these complete figures—you will agree that 'Indocin' does Extend All the Margin of Safety—in the management of arthritic disorders."

With a complete and candid explanation on side effects such as this, it is difficult to see how any physician can refuse to believe that Whenever the Problem Is Oppressive Joint Pain Associated With Heat, Redness, Tenderness, and Swelling—

When the Muscles Around an Inflamed Joint Are in Spasm Causing a Limitation in Motion—

Whether the Tentative Diagnosis Is Osteoarthritis of the Hip, Gout, Rheumatoid Arthritis, Rheumatoid Spondylitis, or Just Plain Musculoskeletal Aches and Stiffness—

For Short-Term Use in Acute Conditions or Long-Term Use in Chronic Conditions—

'Indocin' Will Afford Relief to Three Out of Four Patients Effectively—

With an Extended Margin of Safety—

Probably With Fewer Tablets—

and, Therefore, Less Cost—

With Less Dosage Adjustment—

and, Therefore, Fewer Problems for Both the Physician and the Patient Than Any Other Currently Available Product.

Tell 'Em Again, and Again, and Again.

Tell 'Em Until They Are Sold and Stay Sold!

BULLETIN No. 93, JULY 28, 1965

To: All Western District Sales Associates.
From: H. Glassner.
Subject: Profit Improvement Promotional Program 'Indocin', August, 1965.

All reports indicate that this one is a Real Winner. Our dollar volume on 'Indocin' in June was basically the automatic shipments. Therefore, these figures are of limited value in assessing individual sales performance as regards repeat orders. Instead, please rely on the weekly tabulations in Angel Town Topics to measure your rate of progress on 'Indocin'. Pick up ten or fifteen new prescribers each week on 'Indocin' and you'll move to the top of your group.

Obviously, 'Indocin' sales greatly Exceed all initial sales forecasts. New revised projections are being developed at West Point. These will be more in line with actual sales experience. Sometime prior to the end of August, your revised 1965 objective on 'Indocin' will be forwarded to you. My guess in that our original objective will be tripled. Mr. Klodt just hates to lose any bet. The best way to beat this—or any other objective—is to continue to sell H— out of 'Indocin'.

It is imperative to do this because time is going to run out. One and probably two additional red-hot items are scheduled for release by October 1. Obviously, these new products will also require and get our all-out effort at the time of

their release. In addition, it is reported in trade journals that both Upjohn and Parke Davis are reaching the final stages of research on anti-inflammatory products of their own. Those, as I understand it, are nonsteroidal.

Obviously, this leaves no time to procrastinate on 'Indocin'. We must establish 'Indicin' firmly during the next sixty days—or it will be too late!

In August, here's what we have to work with:

	R.D. value
150 'Indocin' 25 mg.—21's (3150 tablets)	$225
50 'Indocin' 25 mg. (3 x 6) (900 tablets)	63
150 'Indocin' Detail Folders	35
150 'Indocin' Folder-Index Cards	15
150 'Indocin' Dosage Cards	9

Add to this figure the cost of having you make 139 to 140 presentations on 'Indocin' this month, plus the cost of journal ads and direct mail necessary to support your efforts in your territory. Then, as a businessman—ask yourself how many dollars in 'Indocin' sales You need to get back to make enough profit to plow $32.0 million in to Research to give You new products.

Before you make any call on 'Indocin' in August, ask yourself these questions:

1. Why am I calling on this physician?
2. What is he presently using in lieu of 'Indocin'?
3. What hits his "hot button" . . . fear, effectiveness, safety, price, etc.
4. Just what am I going to tell him today that will make it imperative for him to Prescribe 'Indocin' Today?

After you have made that call, ask yourself just one question to measure your own effectiveness:

1. Based on what I just did in that office . . . How many tablets of 'Indocin' is that physician likely to prescribe this month?

Let's face it! 'Indocin' is a superior therapeutic agent. The documented F&DA approved claims indicate that 'Indocin' relieves the pain, reduces the stiffness, tenderness, and fever—and increase joint mobility in patients treated with 'Indocin' when the diagnosis has been acute and chronic rheumatoid arthritis, osteoarthritis of the hip, ankylosing spondylitis, and acute and chronic gout. These clinical entities are the toughest, most resistant, most prolonged rheumatic lesions the specialist is likely to encounter.

Since 'Indocin' is known to convey effective relief from the pain and inflammation of these most difficult lesions and to do this with an extended margin of safety, it is obvious that 'Indocin' will work in that whole host of rheumatic crocks and cruds which every General Practitioner, Internist, and Orthopedic Surgeon sees everyday in his practice. For these entities he is presently prescribing steoids, aminopyrine-like butasones, aspirin, or limited analgesics like Darvon and the almost worthless muscle relaxants.

Remember, until 'Indocin,' the physician who wished to use medication had only four classes of drugs available to him:

1. Aspirin or simple aspirin-like analgesics which only relieve pain.
2. Steroids which only relieve inflammation.
3. Butasolidin or other aminopyrine derivatives which are too dangerous for prolonged use.
4. Muscle relaxants which rarely work and, at best, only temporarily relieve.

Today, 'Indocin' effectively does all of these things with just one tablet. 'Indocin' is anti-inflammatory. 'Indocin' is analgesic. 'Indocin' breaks up the pain—spasm—pain cycle, thus increasing joint mobility. Yet, 'Indocin' is neither a steroid nor an aminopyrine derivative—but, rather, a unique, new chemical entity which affords an extended margin of safety in the long-term management of arthritic disorders.

Run scared! Get a sense of urgency into every presentation. When you do, you will convince the physician that—

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling. . . .

When the muscles around an inflamed joint are in spasm causing a limitation in motion. . . .

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain musculoskeletal aches and stiffness. . . .

For short-term use in acute conditions or long-term use in chronic conditions. . . .

'Indocin' will afford relief to 3 out of 4 patients effectively. . . .

With an extended margin of safety . . . probably with fewer tablets . . . and, therefore, at less cost . . . with less dosage adjustment . . . and, therefore, fewer problems for both the physician and the patient than any other currently available product.

You've told this story now, probably 130 times. The physician, however, has heard it only once. So, go back and tell it again and again and again and again, until it is indelibly impressed in his mind and he starts—and continues—to prescribe 'Indocin.'

Let's go!

BULLETIN No. 95, AUGUST 4, 1965

To: All Western District Sales Associates.
From: H. Glassner.
Subject: Profit Improvement Promotional Program—'Indocin.'

Bill Benedict brought back from the meeting in Chicago a group of the most common questions you have been asked about 'Indocin.' Unfortunately, we do not have all of the answers. As you get questions—shoot them in and we'll try our best to get you an answer you can use.

1. What is the mode of action of 'Indocin?' Where does it work?
   'Indocin' exerts its anti-inflammatory—analgesic and antipyretic effects at the tissue level. How it works is not yet clear since chemically Indomethacin represents the first of a whole new group of compounds.
2. How can an analgesic cause headache?
   This phenomenon also is not yet clear. The direct central action of 'Indocin' is very slight. It is presently postulated that 'Indocin' may exert some peripheral vaso dilatory effect . . . which causes a mild headache-type central reflex.
3. Will 'Indocin' work in any musculoskeletal inflammatory reaction?
   Yes. However, in submitting the original claims for an approved N.D.A. . . . it was obviously important to demonstrate both the effectiveness and safety of 'Indocin' in the toughest and most resistant cases. These are the only cases that top-notch investigators will follow. 'Indocin' works effectively in those resistant cases. Other specific claims, such as bursitis, fibrositis, etc., will be forthcoming. 'Indocin' works in these entities. From the point of view, of daily clincal practice, the physican himself will expand the uses to suit his practice. 'Indocin,' however, is a broad-spectrum anti-inflammatory agent which is specific for inflammatory lesions of the musculoskeletal system.
4. Is 'Indocin' indicated for bronchial asthma?
   No. Bronchial asthma is an acute or chronic allergic disease. While there is lots of inflammation present . . . it takes a specific anti-allergic agent such as 'Periactin' or 'Decadron' to work effectively in bronchial asthma.
5. Why is the maximum dose of 'Indocin' only 200 mg./day?
   That is all it takes to get the job done. Going beyond that limit does not appreciably increase the effectiveness of 'Indocin' and does seem to increase the severity of the side effects one may anticipate.
6. Does 'Indocin' alter the pH of body fluids or urine?
   No. 'Indocin' has no affect on the pH of blood or urine.
7. Can 'Indocin' be safely administered to a diabetic?
   Yes. 'Indocin' has no effect on glucose, metabolism or glucose tolerance in either the normal patient or a diabetic patient.
8. Can 'Indocin' be safely administered to a patient who is taking anticoagulants? Does it affect prothrombin time?
   'Indocin' has no affect on prothrombin time. 'Indocin' can be safely administered to a patient who is also taking anticoagulants.
9. Will antiacids interfere with absorption of 'Indocin' from the G.I. tract?
   No. Antiacids may be administered concomitantly with 'Indocin.'
10. When will reprints on 'Indocin' be available?
    As soon as the papers are published in journals of wide circulation . . . probably within the next three to six months.

It is becoming evident that the greatest mistake we can make with 'Indocin' is NOT to remind the physician that--

Whenever the Problem is Oppressive Joint Pain Associated With Heat, Redness, Tenderness, and Swelling. . .

When the Muscles Around an Inflammed Joint Are in Spasm Causing Limitation of Motion. . .

Whether the Tentative Diagnosis is osteoarthritis of the Hip, Gout, Rheumatoid Arthritis, Rheumatoid, Spondylitis, or Just Plan Musculoskeletal Aches and Stiffness. . .

For Short-Term Use in Acute Conditions or Long-Term Use in Chronic Conditions.

'Indocin' Will Afford Relief to 3 Out of 4 Patriots Effectively. . . .

With an Extended Margin of Safety. . .

Probably With Fewer Capsules. . .

And, Therefore, Less Cost. . .

With Less Dosage Adjustment. . .

And, Therefore, Fewer Problems for Both the Physician and the Patient Than Any Other Currently Available Product.

This Is a Big One. Keep Sellin' It!

BULLETIN No. 23, APRIL 5, 1967

To: All sales Associates.
From: H. Glassner.
Subject: Profit Improvement Promotional Program Indocin-April Promotion.

During 1966, the Western Region with 10.8% of the nations manpower, contributed 10.3% of the nation's total volume on Indocin.

That was not very good.

Now for the first two months of 1967, we have contributed only 10.1% of the nation's total volume on Indocin.

That is even worse.

While for two months of 1967, the nation had a 32.6% increase in Indocin sales, the Western Region had only a 25.0% increase.

For the two month period we are 0.6% behind our Profit Plan Objective on Indocin.

District rankings, giving equal weight to percent of objective attained and percentage incease over 1966 sales follow. Remember 66.6% of objective is par.

District	Total sales	Percent of quantity of objective attained	Percent plus/minus 2 months of 1966
Perttula's Pirates	$105,285	72.7	35.3
Westmoreland's Wranglers	71,999	73.3	31.2
Benedict's Bombers	92,875	67.8	31.3
Waddle's Warriors	124,867	69.2	21.6
Feudin Hatfields	63,151	60.6	24.6
McCabe's Maulers	70,224	60.8	20.9
Lundahl's Lumberjacks	89,892	56.8	12.0
Region		66.0	25.0
Nation			32.6

Top three and low three volumes among our regular representatives for the two month period were turned in by;

1. Joe Powell, $18218.
2. Rich Mazziotti, $16331.
3. Bud Iverson, $13002.

68. Roger, Hillman, $4406.
69. Dan Taylor, $3225.
70. Fred Mansho, $3027.

Tabulations of two month sales on Indocin, ranked by the percentage of objective attained, for all regular territories is attached.

The Tools

During April you will be working with the following assortment:

75 Indocin 25mg (3x6)—1350 Capsules	$98
25 Indocin 25mg—21's—525 Casules	37
50 Indocin Folder Index Cards 296L	5
Total	140

So far in 1967, Joe Powell has gotten almost a 70 fold return on his monthly Indocin promotional assortment.

What is your return on the investment of promotional material which you have made?

The Plan

Our objective in April and every month in 1967 is to narrow the gap between your sales and the top sales in the Region.

This can best be done by "Selective Detailing"—bringing the right product to the right physician with the right theme. The theme must be one that allays his fears, or makes his therapy more effective, safer, or more economical.

Indocin is an easy product to be selective about. Sales and Marketing Research studies show that general practitioners and internists prescribe more than 90% of all the nonsteroidal anti-inflammatory, anti-arthritic agents used. Therefore, in April. . . . pin point your shots. Select no more than 30 general practioners and/or internists for a hard hitting detail on Indocin.

Let's be realistic. By this time most physicians have seen, read, or heard about the report in the New England Journal of Medicine and/or the Wall Street Journal.

The general practitioner and internist in private practice is a mature, pragmatic individual. He realizes that his patients can not afford the luxury of "Ivory Tower" thinking.

The arthritic he sees in his daily office practice demands prompt relief of pain.

The arthritic he sees in daily office practice demands an anti-inflammatory agent that will relieve swelling and increase joint mobility so that he can become productive.

The private practitioner realizes that the arthritic he sees in daily practice will probably be taking medication on a chronic basis. He wants a preparation that can be taken for the long term with as few hazardous side effects as possible.

Indocin is an effective anti-inflammatory agent that is suitable for long term as well as short term use in adult patients who are not pregnant.

Indocin has been found effective in relieving pain; reducing fever, swelling, and tenderness; and increasing mobility in patients with rheumatoid arthritis, rheumatoid spondylitis; osteo arthritis of the hip and gout.

Indocin is much more than a simple analgesic. It is a unique chemical entity unrelated to aspirin, steroids, colchrine or phenylbutozine.

Let's stand on our little old two feet this month and sell the benefits of Indocin.

When some hard-nosed physician brings up one of the recent "controlled" studies reported in the Wall Street Journal . . . Rich Mazziotti stops him cold by opening the Indocin literature to the bibliography and simply asking . . .

"Doctor, can all of these physicians of impeccable reputation really be wrong?

"Doctor, can your own experience with Indocin in your own practice these past 33 months really be wrong?"

Take off the kid gloves. If he wants to use aspirin as base line therapy, let him use it. Chances are the patient is already taking aspirin. He has come to the physician because aspirin alone is not affording satisfactory, optimal effects.

When aspirin alone is not enough . . . Indocin is the logical prescription of choice.

District Managers report that because Edecrin was on primary promotion in March, most of you still have a supply of the leave detail piece sent for use in March. It is a good one. Use it in April to show general practitioners how to maximize the benefits of Indocin for their patients. If you do this effectively, your pockets can swell with extra bonus bucks.

Let's go back down to selling Indocin again.

INDOCIN, JANUARY THROUGH FEBRUARY 1967

Group	Volume	Percent
Lachman	$7,887	79
Lockett	9,235	73
Putnam	8,450	70
Lewine	8,100	70
Tonkyro	8,633	67
Groos	10,475	60
Total	71,999	73
Perttula's group:		
Mazziotti	16,331	91
Woolley	11,160	83
Houts	10,101	71
Number 2626	8,456	71
Wolfe	7,136	70
Washington	5,662	69
Mustard	6,017	69
Mickelson	7,930	66
Edwards	9,638	66
Hammang	8,311	66
Brekke	11,914	62
Total	105,285	73
Waddle's group:		
Powell	18,218	83
Iverson	13,002	77
Bentley	10,118	71
Smith	10,482	69
Pies	10,890	62
Hart	7,053	65
Cargile	8,144	64
Ginger	11,588	63
Hilliker	12,045	62
Yarborough	8,632	61
Kohls	8,199	58
Total	124,868	69
Benedict's group:		
Brown	8,846	77
Nordquist	5,109	72
Alfano	9,282	70
DuBois	9,469	69
Solari	7,182	68
Lazarus	4,159	68
Lawing	9,052	67
Vitt	7,846	66
Strinz	6,315	66
Benedict's group—Continued		
Richardson	$6,908	64
Blake	8,870	64
Filler	8,584	64
Total	92,876	68
Lundahl's group:		
Walker	7,892	64
Collins	6,110	64
Knight	6,835	63
Doody	7,510	62
Nolan	5,796	60
Locke	9,018	58
Hydeman	9,392	58
Harris	5,817	54
Peper	9,061	52
Stewart	8,579	52
Lanciotti	5,006	51
Wessells	7,879	50
Total	89,893	57
McCabe's group:		
Mele	7,335	74
Gray	12,851	66
Chalmers	7,984	66
Ayala	7,365	61
Chazankin	4,985	61
Callan	9,184	60
Kearney	5,557	57
Hillman	4,406	53
No. 2720	6,197	51
Total	70,225	61
Hatfield's group:		
Furr	4,456	65
O'Brien	8,456	64
Burgess	7,052	63
Allen	8,600	63
Pederson	5,910	60
Mansho	3,027	59
Koberstein	9,446	57
Baker	4,196	52
Taylor	3,225	62
Total	63,151	61
Region total	618,955	66

BULLETIN No. 66, JULY 17, 1967

To: All Western Region Sales Associates.
From: H. Glassner
Subject: Profit-Improvement Promotional Program, 'Indocin'.

PAST PERFORMANCE

For five months of 1966, with 10.8% of the national manpower, the Western Region has contributed 10.7% of national sales on 'Indocin'.

While the nation was 22.6% ahead of the same period in 1966, this region was 24.7% ahead.

At the end of five months, we were running about 2.5% ahead of our Profit Plan for 'Indocin'.

These figures, of course, include the orders that were dated in April and May. However, package sales for June indicate we are again increasing sales of 'Indocin'. It appears the bad publicity we had early in the second quarter is now behind us.

The standings, by district, for five months follow:

District	Amount	Percent of objective attained	Percent, plus/minus 1966
1. Westmoreland's Wranglers	$187,687	95	36.9
2. Perttula's Pirates	274,432	93	30.8
3. Benedict's Bombers	253,019	91	30.1
4. Waddle's Warriors	334,788	91	26.8
5. Feudin' Hatfields	173,145	81	25.1
6. McCabe's Maulers	182,489	77	15.0
7. Lundahl's Lumberjacks	240,614	74	10.3
Region		86	24.7
Nation			22.6

Top three sales volumes in the region for five months on 'Indocin' were turned in by:

1. Joe Powell, $46,024.
2. Rich Mazziotti, $36,560.
3. Dean Hilliker, $35.884.

THE TOOLS

During the months of July and August, you will be working with the following assortment:

125 'Indocin' 25 mg. (3 × 66)—2250 capsules	$140
50 'Indocin' 25 mg.–21's—1050 capsules	70
50 'Indocin' Folder-Index Cards, 539L	10
2 'Indocin' Permanent Detail Piece, 612L	20
250 'Indocin' Telephone Pads	30
50 'Indocin' "How to Use Leaflets?"	10
Total	280

Joe Powell is making an average monthly assortment return $60 for every $1 he expands in promotional material.

What is your batting average?

THE PLAN

A recent report from Sales & Marketing Research on the reputation and usage of various drugs in severe rheumatoid arthritis points the way to increased opportunities.

In this study, physicians identified any patient with severe rheumatoid arthritis as one afflicted with pain and crippling so severe he could not perform his usual activties, often needed to be cared for by others, and had objective evidence of severe disease. The survey found the following attitudes among general practitioners and internists relative to severe rheumatoid arthritis:

1. 'Indocin' held only 19% of the severe rheumatoid arthritic market.
2. 'Indocin' was the second most often prescribed product in this market.
3. Eight out of ten physicians questioned, sometimes use 'Indocin' in the treatment of severe rhematoid arthritis, yet seldom used it as the first drug they prescribed.
4. Almost five out of ten physicians questioned do not use 'Indocin' as either the first or the second drug to treat severe rheumatoid arthritis.
5. Two other products, aspirin and Darvon, have 48% of the severe rheumatoid arthritic market.
6. Eighteen per cent of the physicians questioned treated all of their severe rheumatoid arthritic patients with aspirin. Yet, G.I. side effects were considered as a bad characteristic of aspirin more frequently than of 'Indocin'.
7. Only aspirin had a better reputation for efficacy and few side effects than did 'Indocin'. Darvon has a more favorable reputation for fewer side effects but a less favorable reputation for efficacy than does 'Indocin'.
8. Butazones, corticoids, and gold salts, hold 33% of the severe rheumatoid arthritic market. Yet, these more potent products have a less favorable reputation among physicians using them for efficacy and side effects than does 'Indocin'.

Obviously, we have done a good job of selling 'Indocin' for long-term management of chronic rheumatoid arthritis. Now, we must convince our physicians to use 'Indocin' for short, severe, flare-ups.

There is room for continued growth of 'Indocin' in the treatment of severe rheumatoid arthritis—where pain and crippling are so severe that the patient cannot function normally. This growth can come from two areas:

1. From the many physicians who prescribe therapy which is "more potent" than therapy with 'Indocin' (i.e. butazones, steroids, and gold) before trying 'Indocin', and

2. From those severely afflicted patients who are not adequately controlled by aspirin or Darvon, i.e. when pain-killers no longer give adequate control or when they only kill pain without reducing inflammation or improving joint mobility. . . . 'Indocin' should be tried promptly or even tried first.

Remember, and make sure your physicians realize that 'Indocin' is an effective anti-inflammatory agent that is suitable for short-term as well as long-term use in adult patients.

Remember, and make sure your physicians realize that unlike aspirin and Darvon 'Indocin' has been found effective in not only relieving pain but reducing fever swelling, and tenderness . . . and increasing joint mobility in the symptomatic treatment of rheumatoid arthritis.

Remember, also, and be sure your physicians realize that for patients with acute, severe rheumatoid arthritis, or acute flares of chronic rheumatoid arthritis, the total daily dose of 'Indocin' may be increased by one capsule per day until a satisfactory response is obtained or a total daily dose of six to eight capsules a day is reached.

We have not really scratched the surface on this one yet.

Let's start digging this month.

INDOCIN, JANUARY THROUGH MAY 1967

	Volume	Percent
Westmoreland's group:		
Lachman	$19,936	98
Putnam	23,413	95
Lockett	24,007	92
Tonkyro	24,020	91
Lewine	21,053	89
Adams	27,512	78
Group	189,687	95
Pertulla's group:		
Mazziotti	36,560	100
Woolley	27,587	100
Mustard	17,359	98
Edwards	29,358	98
Washington	15,939	95
Groos	22,290	91
Mickelson	22,247	91
Wolfe	18,725	90
Houts	26,030	89
Hammang	22,697	88
Brekke	31,365	80
Group	274,432	93
Waddle's group:		
Powell	46,024	103
Pies	32,743	101
Smith	29,955	96
Iverson	32,130	9/
Hilliker	35,884	91
Bentley	25,524	84
Hart	19,119	86
Cargile	21,486	83
Ginger	30,876	83
Yarborough	22,767	79
Kohls	21,895	75
Group	334,788	91
Benedict's group:		
Brown	22,886	98
Lawing	27,175	98
Strinz	18,607	95
Alfano	25,585	95
Nordquist	13,579	93
DuBois	25,031	89
Solari	18,847	88
Blake	24,775	87
Filler	23,783	87
Richardson	18,797	86
Benedict's group—Continued		
Vitt	19,958	83
Lazarus	10,325	83
Group	253,019	91
Lundahl's group:		
Collins	18,943	98
Walker	22,593	90
Locke	25,379	81
Doody	20,018	81
Hydeman	24,858	76
Knight	16,863	76
Nolan	14,771	75
Stewart	22,708	68
Lanciotti	13,053	67
Harris	16,875	66
Peper	22,992	65
Wessells	21 006	65
Group	240,614	74
McCabe's group:		
Mele	18,577	92
Chalmers	21,725	87
Gray	33,357	84
Ayala	19,175	78
Kearney	15,056	75
Chazankin	12,536	75
Callan	23,836	74
Nylund	17,330	70
Hillman	10,807	63
Group	182,489	77
Hatfield's group:		
Furr	12,703	91
Pederson	16,695	83
Allen	21,884	83
Burgess	21,186	83
O'Brien	21,009	82
Baker	15,208	78
Mansho	7,845	74
Koberstein	22,885	74
Taylor	9,276	73
Group	173,145	81
Region	1,649,075	86

BULLETIN No. 74, SEPTEMBER 5, 1967

To: All Western Region Sales Associates.
From: H. Glassner.
Subject: Profit Improvement Promotional Program, 'Indocin.'

"If it doesn't work in a week, forget it."

Now that's a clever slogan. It really should say, "If it does work in a week, you had better really forget it."

Here are some direct quotes from the current package circular for Butazolidin.

1. "Important Note. Butazolidin brand of phenylbutazone, cannot be considered a simple analgesic and should never be administered casually. Each patient should be carefully evaluated before treatment is started and should remain constantly under close supervision of the physician. . . ."

2. "Contraindications. Butazolidin, brand of phenylbutazone, is contraindicated in the presence of edema and in cases in which there is danger of cardiac decompensation. . . ."

Now, how many older patients . . . the patients with most of the aches and pains . . . the real crocks and cruds seen in everyday daily practice . . . just how many of these patients do not have some degree of cardiac decompensation or some degree of edema?

Yet, the term "contraindication" has medico-legal connotations. This part of the country has the highest rate of malpractice suits and, therefore, the highest rate of malpractice insurance. Why add fuel to the fire?

3. "Precautions. Patients receiving Butazolidin, brand of phenylbutazone, should remain under close supervision of the physician and should be warned to report immediately the recurrence of fever, sore throat, lesions in the mouth, or black or tarry stools. Specifically, it is recommended that periodic visits with the physician include:

a. Verbal and physical examinations for indications of toxic reactions.
b. Check of patient's weight to determine significant water retention.
c. Complete blood counts at weekly intervals during the early phase of therapy and at intervals of two weeks thereafter to guard against the possibility of blood dyscrasia."

A complete blood count costs at least $7 to $10. That makes therapy much, much too expensive.

Let's take the kid gloves off and start slugging it out.

Let's stress the balance between efficacy and safety of 'Indocin'. Our literature doesn't say anything about complete blood counts under precautions or contraindications.

The annoying G.I. side effects of 'Indocin' can be easily minimized by simple dosage adjustment, taking the dosage with food, milk, or antacid.

Let's get back to selling 'Indocin'. Be certain that every physician understands that

Wherever there is pain, inflammation, and swelling in or around the joint with a resultant limitation of motion as there is in rheumatoid arthritis, ankylosing spondylitis, acute attacks of gout, or osteoarthritis of the hip—

Whether the condition is acute or chronic . . .

Therapy with 'Indocin' usually—

Relieves pain, reduces inflammation, and increases joint mobility on a simple dosage regimen that is relatively safe, often dramatically rapid in effect, and usually most economical.

'Indocin' is a great drug. Promote it like it was.

BULLETIN No. 77, SEPTEMBER 11, 1967

To: All Western Region Sales Associates.
From: H. Glassner.
Subject: *Profit Improvement Promotional Program, 'Indocin.'*

Let's dare to compare.

In the management of inflammatory lesions of the musculoskeletal system where there is pain, inflammation, and limitation of motion—as there is in rheumatoid arthritis, osteoarthritis of the hip, ankylosing spondylitis, and acute gout—what choice does the physician really have if he does not prescribe 'INDOCIN'?

Sure, he can use aspirin. But, the patient has probably already used aspirin before he visits his physician. Furthermore, no less an authority than Dr. Howard Polley at the Mayo Clinic has said

". . . I wouldn't put 'Indocin' in the category of aspirin. I think it is more potent. But, if indomethacin is as good as aspirin, that is a pretty good claim in my view. That is a recommendation for indomethacin. . . ."

If he is a gambling sole—and almost no physician ever likes to gamble with his patient's welfare—he can prescribe Butazolidin. However, the current edition of the Goodman and Gilman, on pages 338–339, states the following about Butazolidin.

". . . Phenylbutazone is poorly tolerated by many patients. Some type of side effect is noted in 10% to 45% of patients, and medication may have to be discontinued in 10% to 15%. Nausea, vomiting, epigastric discomfort and skin rashes are the most frequently reported untoward effects from phenylbutazone. . . ."

". . . Its use should be restricted to short-term therapy of not more than one week during any one treatment period. Even then the incidence of disturbing side effects is about 10%. . . ."

He can prescribe steroids, the most potent anti-inflammatory compounds presently available. But there is general widespread agreement among qualified clinicians that steroids.

1. Should never be the initial agent used to treat rheumatoid arthritis.
2. Should be used only after a conscientious and unhurried trial of conservative measures fails to achieve satisfactory results.
3. Should not constitute the only measure of treatment.

If he wants just analgesic effect, Darvon will work just as well as aspirin, but Darvon has little or no anti-inflammatory activity. Its use is purely palliative. At best, treatment covers only one symptom.

Let's be rational. Do yourself and your physicians a favor. Before you do anything else, as soon as you get into the office, make sure that he realizes that

When there is pain, inflammation, and limitation of motion in or around a joint as there is in rheumatoid arthritis, ankylosing spondylitis, acute gout or osteoarthritis of the hip,
Whether the condition is acute or chronic,
For short-term or long-term use,
Therapy with 'Indocin' usually
Relieves Pain,
Reduces Swelling, and
Improves Joint Mobility

on a flexible dosage regimen that is usually effective, usually, safe, and always economical.

Remember, the product credit value of 'Indocin' is now 1.0. If your 'Indocin' sales are just average, you have automatically increased your income by $22 per month.

Now, every extra bottle of 1000 'Indocin' that you sell is worth an extra $2.80 in incentive payments.

Go get it.

BULLETIN No. 80, SEPTEMBER 13, 1967

To: All Sales Associates in the Western Region.
From: H. Glassner.
Subject: *Profit Improvement Promotional Program, 'Indocin.'*

If you are a timid sole, if you are a cautious 'Indocin' detailer, you can still find some Powerful Selling Sentences right in the F&DA approved package circular.

How about using these?

"In acute rheumatoid arthritis, or in acute flares of chronic rheumatoid arthritis, prompt improvement with relief of pain, tenderness, swelling, and stiffness will usually occur."

"In many patients with chronic rheumatoid arthritis, 'Indocin' produces a significant decrease in pain and stiffness within forty-eight hours. . . ."

" 'Indocin' . . . has anti-inflammatory, analgesic, and antipyretic activity. It has a unique chemical structure which differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds, and cholchicine. Unlike corticosteroids, it has no effect on pituitary or adrenal function."

Use one, use two, or use 'em all. But be sure he understands that

Whenever there is pain, inflammation, and limitation of motion in and around a joint—as there is in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis of this hip, and gout . . .

whether the condition is acute or chronic . . .

whether therapy is to be long-term or short-term . . .

therapy with 'Indocin'

relieves pain,

reduces inflammation,

and improves joint mobility

on a flexible dosage schedule that is usually effective, usually safe, and quite economical.

Remember, if your sales of 'Indocin' are just average, the new product credit value for 'Indocin' gives you an automatic $22 per month increase in incentive payments plus the opportunity to earn $2.80 extra for every bottle of 1000 'Indocin' you sell over your present average sales.

BULLETIN No. 85, SEPTEMBER 27, 1967

To: All Western Region Sales Associates.
From: H. Glassner.
Subject: *Profit Improvement Promotional Program, 'Indocin.'*

Don Epperson is brand new. He hasn't even been assigned to a territory yet. He is still waiting to go to West Point to complete his Basic Training. He doesn't know any better than to spend enough time putting a hard-hitting story on 'Indocin' together and then deliver it with conviction, enthusiasm, and force. He is temporarily working in a vacant territory.

Howard Perttula brought the following detail back, after working with Don just two days. Try it. It might put you in the top ten before Don gets assigned. By that time, he should be crowding our Top Ten Club. The selling time for this detail is less than three (3) minutes.

"Doctor, in the management of pain, inflammation, and limitation of motion associated with musculoskeletal diseases, there are many choices of therapy.

Basically, at one end of the continuum is Aspirin . . . at the other and are steroids.

In between these two extremes, you can choose between phenylbutazone and 'Indocin'.

'Indocin' is chemically unique. It is not a steroid. It is not an aminopyrine derivative. Therefore it is distinctly different from phenylbutazone. Indeed, unlike phenylbutazone when 'Indocin' is used for prolonged therapy, the patient does not need to pay for periodic complete blood counts.

Most of the adverse reactions which occur with 'Indocin' are common with any anti-rheumatic drug. They usually are transient, easily controlled, and often disappear on continued treatment.

Yet, 'Indocin' is not a simple analgesic. 'Indocin' is a potent analgesic with pronounced anti-inflammatory properties which frequently affords prompt relief of acute rheumatoid arthritis and increased joint mobility within forty-eight (48) hours. In fact, the action of 'Indocin' is often so rapid that when it is used in an acute attack of gout, a marked reduction of pain often occurs within two to four hours.

Whenever the patient's problem involves pain, inflammation, redness, swelling, and limitation of motion in or around the joint . . . . as in rheumatoid arthritis, osteoarthritis of the hip, ankylosing spondylitis, or gout—

whether the condition is chronic or acute,

whether therapy is to be short or prolonged,

'Indocin' usually provides a reduction in swelling, relief of pain.

Since most rheumatoid arthritic patients who present themselves to you with such problems are having an acute flare-up of their disease, you can maximize the benefits of 'Indocin' by starting the patient on one or two capsules of 'Indocin' three times a day . . . pushing the dose to a maximum of six capsules . . . until relief is obtained and then gradually tapering the patient off to the usual maintenance dose of two or three capsules a day.

Gastric irritation can be minimized by giving the dose of 'Indocin' after meals.

Doctor, will you use 'Indocin' in the management of these arthritic disorders either after Aspirin or before Steroids, so your patient can benefit from 'Indocin' that much sooner?"

Remember, every bottle of 1000 'Indocin' that you sell, over your normal average, is now worth an additional $2.80 in incentive payments.

Pile it in! ! !

Dr. McCLEERY. This Bulletin No. 83 advises the detail man to tell the physician:

Doctor, I'm certain that in your busy practice no day passes without several patients seeking your help from the misery inflicted by painful, reddened, swollen, feverish joints—the classic signs of inflammation.

The bulletin goes on to promote Indocin for "pain in the muscles." It urges the detail man to "convince" the physician that Indocin should be used "when the muscles around an inflamed joint are in spasm causing a limitation in motion" and for "just plain muscoskeletal [sic] aches and stiffness * * *"

The unwarranted claims I have just mentioned appear repetitively in other bulletins of this same introductory time period. We regard these claims as outside the limits of indications in the approved labeling and therefore seriously misleading. In this connection, Bulletin No. 87, July 20, 1965, contains this statement of admission:

In fact, our guys are using a real expanded claim for "Indocin" on inflammation. They are consistently telling their doctors that * * *

They repeat the quotes similar to the ones I mentioned just above.

Senator NELSON. So in the drug company's own bulletin this sentence is a confession that they are making claims over and above those approved by the FDA, is that not correct?

Dr. McCLEERY. Yes, it is correct that that is what these bulletins say.

Senator NELSON. Please go ahead.

Dr. McCLEERY. It appears quite clear that the detail men were being told to influence physicians to use Indocin for unapproved uses.

But the instruction to Merck detail men did not stop with the promotion of unapproved uses. The detail men were given slanted information to deemphasize side effects and other warnings.

Mr. Chairman, in the interest of saving the committee's time I will not recount all of the information in the Indocin package insert on contraindications, precautions, adverse reactions, and other warnings. In the composite, all of this information suggests that Indocin must be used cautiously, if at all, and with the expectation that serious side effects may occur.

Notwithstanding all of the warning advice in the package insert, the bulletins representing the period July 12 to August 4, 1965, instructed Merck detail men to convince physicians that "therapy with Indocin is safer." The implication was that Indocin is even safer than aspirin. The physician was told that the drug is contraindicated in pregnancy but nothing was said in the bulletins of instructions about its being contraindicated in children. The instructions stated that the only contraindications are pregnancy, ulcerative colitis, active peptic ulcer, and gastritis. This was false.

The instructions went on to say:

The other side effects are not serious. Some patients on therapy with Indocin may experience headache, dizziness or lightheadedness, and even some minor G. I. disturbances.

What the instructions did not disclose here were many serious side effects listed in the package insert. One such was that—

> Indocin may cause single or multiple ulceration of the stomach, duodenum, or small intestine. There have been reports of severe bleeding and of perforation with a few fatalities.

Some other side effects listed in the package insert are drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritis, urticaria, angioneurotic edema, skin rashes, and edema.

In Bulletin No. 88, issued July 21, 1965, it was suggested that the detail men use this sales approach:

> So, doctor, let's examine the relative lack of side effects of "Indocin."
> In six out of ten patients on "Indocin," you need anticipate no adverse effects whatsoever.
> In two out of three of these ten patients, some bothersome effects might occur. Bothersome is probably as severe an adjective as we can use to describe these effects because in most patients they are tolerable, and transient.

Mr. Chairman, as you know from our testimony last May there were a series of events that occurred between 1965 and 1967 which involved our dealing with Merck regarding its advertising and promotion of Indocin. The Assistant General Counsel, Food and Drugs Division, of the Deparment of Health, Education, and Welfare spoke publicly in October 1966 regarding our opinion as to the misleading nature of an Indocin advertisement which appeared in the Journal of the American Medical Association and elsewhere. Conferences were held with Mr. Henry W. Gadsden and his associates in the Merck managament in November 1966.

Senator NELSON. So there is not any requirement on the part of the American Medical Association that the drug company make claims in their advertising in compliance with approved indications by the FDA?

Dr. MCCLEERY. I don't believe that their code of approval of advertising copy includes the requirement that it conform to the package insert. They do have their own code, which they follow. And they state in each journal that it is applied to all advertising submitted to the journal before an ad is approved.

Senator NELSON. Do you mean to say that the American Medical Association, the AMA Journal, knowing the claim made in an ad in their medical journal goes beyond approved claims by the FDA is still willing to accept that ad?

Dr. MCCLEERY. I would not want to say that the staff of the journal is aware of the information in the package inserts or that they are not, or why they make the judgments they do.

Senator NELSON. So far as you know, they do not require as a matter of advertising policy that the company inserting an ad comply with FDA-approved regulations as to that drug?

Dr. MCCLEERY. So far as I know they do not, but I do not know just what their standards precisely might be.

Senator NELSON. Are you aware of the fact that any number of times ads have been put in the AMA Journal which made claims beyond approved indications by the FDA?

Dr. MCCLEERY. I am aware, Mr. Chairman, that on quite a number of occasions we have felt the necessity to charge ads as false or mis-

leading in our view that have appeared in the Journal of the American Medical Association.

Senator NELSON. But I don't suppose I could expect you to comment on it, but it would seem to me that the great and distinguished medical profession ought to have the integrity to throw out any ad by any drug company that misleads the doctors. If there is anything a doctor ought to be able to rely upon, it is the official publication of the American Medical Association. I would assume that every doctor would say to himself that this is the distinguished leadership of the medical professions speaking to us, and what we say in their journal is honest, and I think it is an incredible disgrace that the AMA Journal wouldn't lay down a rule that any ad you put in here has got to comply with the FDA regulations. It shocks me, and I am ashamed of the leadership of this great profession respecting this kind of business misleading the doctors.

Please go ahead.

Dr. MCCLEERY. Having given the Merck organization notice of our views of the status of their advertising and promotion of Indocin under the Federal Food, Drug, and Cosmetic Act, the firm did take action to correct its journal advertising.

Notwithstanding, we find in Merck instructional bulletins dated between April 5 and September 27, 1967, continued suggestions for open-ended uses and continued minimization of side effects. The bulletins, addressed to all associates western district, still bear the name of the same individual who apparently issued the bulletins back in 1965. There is nothing we see in the 1967 bulletins that suggest the firm had changed its basic philosophy and methods of promotion of Indocin from those employed in 1965.

Mr. Chairman, we have applied the principles of the advertising and labeling regulations in evaluating the Indocin bulletins apparently issued to Merck detail men in 1965 and 1967. Against these principles, we regard the bulletins as false or misleading in many details.

Other features of the bulletins which appear worthy of mention reflect disquieting attitudes of the firm's employees toward the medical profession and to the patient. Some of the statements in point in the bulletins are:

* * * it is obvious that "Indocin" will work in that whole host of rheumatic crocks and cruds which every General Practitioner, Internist, and Orthopedic Surgeon sees everyday in his practice.

Tell 'em again, and again, and again.

Tell 'em until they are sold and stay sold!

For these entities ["rheumatic crocks and cruds"] he [the doctor] is presently prescribing steroids, aminopyrine-like butazones, aspirin, or limited analgesics like Darvon and the almost worthless muscle relaxants.

You've told this story now, probably 130 times. The physician, however, has heard it only once. So, go back and tell it again and again and again and again, until it is indelibly impressed in his mind and he starts—and continues—to prescribe "Indocin." Let's go.

Let's stand on our little old two feet this month and sell the benefits of "Indocin."

Take off the kid gloves. If he wants to use aspirin as base line therapy, let him use it. Chances are the patient is already taking aspirin. He has come to the physician because aspirin alone is not affording satisfactory, optimal effects.

Now, every extra bottle of 1000 "Indocin" that you sell is worth an extra $2.80 in incentive payments. Go get it. Pile it in!!!

Mr. Chairman, if you have any questions I will be glad to answer them to the extent possible.

Senator NELSON. There was one other quote in Bulletin 74 referring again, referring this time to older patients and calling them "The real crocks and cruds." Now that quote is:

> Now, how many older patients, the patients with most of the aches and pains, the real crocks and cruds seen in everyday and daily practice, just how many of these patients do not have some degree of cardiac decompensation and some degree of edema?

For a great and distinguished company to be referring to elderly citizens as "the real crocks and cruds" gives you some idea of the level of their attitude toward the patients. And apparently the attitude of the detail men and all the rest of them. The approved package labeling which I have here is dated effective May 1965; is that correct?

Dr. MCCLEERY. Yes, sir.

Senator NELSON. Is a copy of the package labeling sent by the firm to all the detail men?

Dr. MCCLEERY. Presumably so. It is required. We have no way of knowing for certain the intimate detail.

Senator NELSON. But the FDA does require that that be done?

Dr. MCCLEERY. With every sample of drug that the detail man is given to give to doctors, there is required to be a package insert.

Senator NELSON. So, then, the 1965 instructional bulletins to detail men were issued after the package labeling had been in effect, is that not correct?

Dr. MCCLEERY. Yes, sir.

Senator NELSON. Do you have a listing of all of the unapproved claims made by the company in the various bulletins examined?

Dr. MCCLEERY. I don't have one before me. We have made one, and I have mentioned a number of them in my testimony. I think that that attitude is perhaps exemplified best in the early period of enthusiasm, which might be understandable if not condonable, in the period when a new drug comes on the market. However, it is less understandable in the year 1967, long after that introduction, and after our contacts on the principle of proper promotion of Indocin had led to agreement between the Commissioner and the top officer of Merck. I think the bulletins in 1967 are much more impressive in the way they express the value and indications of Indocin, and also what uses are suggested in this language, presumably by a regional sales manager, to develop copy for oral assertion by individual detail men to the doctor. This is much more subtle than the kind of language in the introductory period, but I think it is also quite instructive of the problem.

I would be glad to point out one or two instances of what I mean if you wish.

Senator NELSON. Please go ahead.

Dr. MCCLEERY. You had made reference just a moment ago to a statement in Bulletin 74 dated September 5, 1967, on the "real crocks and cruds." In the same bulletin in which that statement is made, there is a reference on the second page which runs through, in a very subtle way, the whole pattern of promotion by this method in the time period of 1967. I will quote from it, Mr. Chairman. On page 2 it says——

Senator NELSON. Is that September 5, 1967, Bulletin 74?

Dr. MCCLEERY. Yes, sir; on page 2. It says: "Wherever there is pain, inflammation and swelling in or around the joint with a resultant limitation of motion as there is in rheumatoid arthritis, rheumatoid

(ankylosing) spondylitis, acute attacks of gout, or osteoarthritis of the hips." On the surface, when this goes by quickly, it sounds like it is entirely within the indications described by the approved package labeling. But the fact of the matter is that it is an open-ended statement of indications, because it says "Wherever there is a pain, inflammation and swelling" use this drug, and the only limitation, and it is not a real limitation, is in bringing in the proper indications by the statements "as there is in rheumatoid arthritis." This is not a limiting statement. It only says wherever there is inflammation use Indocin, and there is inflammation in rheumatoid arthritis, and so forth. This runs through the whole time period of 1967.

Senator NELSON. And that statement I read to you previously about the older patients, that is:

Now, how many older patients, patients with most aches and pains, the real crocks and cruds seen in everyday practice, just how many of these patients do not have some degree of cardiac decompensation or degree of edema?

What is that in there for, cardiac decompensation and some edema?

Dr. MCCLEERY. Well, there are competitive drugs which are mentioned throughout the bulletins of this time period. The characteristic of this time period is competitive selling, giving the detail men information which may or may not be proper about the dangers or effectiveness of competitive drugs. One of the competitive drugs does have warnings in its labeling about the possibility of causing edema. Therefore, they are saying that this would limit the value of the competitive drug in this particular class of patient. There is some truth in that.

Senator NELSON. Is it common that you may end up with muscular soreness and tenderness as a consequence of the edema?

Dr. MCCLEERY. That would be difficult to answer, Mr. Chairman. As far as the patient is concerned, he might feel that he had aches in his muscles, because of the swelling, and very likely wouldn't himself localize it to muscle, but just to his lower extremity.

We said in our testimony that there was some slanting of information and I would like, if you wish, to describe what we meant by that statement.

Senator NELSON. Yes, if you would, please.

Dr. MCCLEERY. I mentioned that the need to sell a product by one company in competition with somewhat similar products by other companies creates the need to draw limits of value between it and its competitors' products. This is going on a great deal during this time period.

One of the drugs which has to be discussed, in this competitive way, for the treatment of rheumatoid arthritis and other inflammatory diseases, is plain aspirin. The bulletin of July 7, 1967, Bulletin No. 66, on page 2, is an example of a description of the value of aspirin in comparison with Indocin. It says:

From those severely afflicted patients who are not adequately controlled by aspirin or Darvon, i.e., when pain killers are no longer giving adequate control—

I am sorry, it says—

when pain killers no longer give adequate control or when they only kill pain without reducing inflammation or improving joint mobility, Indocin should be tried promptly or even tried first.

It goes on to say on the same page:

Remember and make sure your physician realizes that, unlike aspirin and Darvon, Indocin has been found effective in not only relieving pain but reducing fever, swelling and tenderness, and increasing joint mobility in the symptomatic treatment of rheumatoid arthritis.

Now, it is very likely true that few doctors would be misled by this description of the effects of aspirin. I don't know how many might be, but in some real sense that is beside the point. The description here is an inaccurate description of the value of aspirin. It puts it in an unfair light in competition, because it puts aspirin together with Darvon, which is not an anti-inflammatory agent, and makes it appear that aspirin also is not an anti-inflammatory agent—that it is only good for the relief of pain. And when it no longer does that one simple thing, then you should turn to Indocin, or even maybe turn to Indocin first, because it implies, if it doesn't directly say, that aspirin only kills paid without reducing inflammation or improving joint mobility.

This is not true of the salicylates, of which aspirin is a member. It is not at all true that unlike aspirin, Indocin has been found effective in not only relieving pain but reducing fever, swelling, and tenderness. Aspirin and other salicylates will also, as has been shown in double-blind studies, reduce not only pain, but fever, swelling, and tenderness. They have reduced swelling in the joints. They have improved joint mobility in double-blind studies. This is a more subtle, much less blatant, approach than the 1965 bulletins, but nevertheless, in our view, slanted and misleading. There are many other examples.

Senator NELSON. You did say a few moments back that you had in going through the bulletins extracted from them all of the claims that were made beyond FDA-approved claims? Did I understand you to say that?

Dr. MCCLEERY. Yes. We have really enumerated most of those, the most important and significant ones in our testimony as far as unapproved indications are concerned.

Senator NELSON. If there are any others that you didn't list in your testimony——

Dr. MCCLEERY. Yes, I have another one in Bulletin 77, September 11, 1967, which is headed on page 1 by the statement: "Let's dare to compare."

Senator NELSON. Pardon?

Dr. MCCLEERY. "Let's dare to compare," and I should mention that this, I feel, reflects a normal and even laudable urge on the part of companies to compete. That is not what we are faulting in this time period, but only describing that this characterizes the nature of the 1967 bulletins.

This one again happens to be on aspirin and salicylates, and it started off by saying, "In the management of inflammatory lesions of the musculoskeletal system, where there is pain, inflammation and limitation of motion," again parenthetically, "as there is in rheumatoid arthritis." It then repeats the proper list of indications. But it is always this combination of the very subtle enlargement created by mentioning inflammation, and whenever there is swelling, "as there is" in the list of indicationed illnesses. This runs all the way through.

Then it turns to an authority that is well known in the field of arthritis and rheumatism, Dr. Howard Polley, of the Mayo Clinic.

But first it suggests, in the language of the bulletin here for the detail man:

> Sure you can use aspirin, but the patient has probably already used aspirin before he visits his physician. Furthermore, no less an authority than Dr. Howard Polley of the Mayo Clinic has said, "I wouldn't put Indocin in the category of aspirin. I think it is more potent. But if Indocin is as good as aspirin, that is a pretty good claim in my view. That is a recommendation for indomethacin."

Now there is a break in the quote of Dr. Polley's opinion. The implication of this quote is, if it were indeed used by a detail man to a doctor, that Dr. Polley is saying that, since indomethacin is as good as aspirin, he would recommend Indocin instead of aspirin. I don't know if that is his view. Whether it is or not, it isn't the view of experts in the field in general. I haven't had a chance to locate this statement by Dr. Polley.

Senator NELSON. You say there is a break in the quote. You mean there was something more said by Dr.—what is his name?

Dr. MCCLEERY. Polley. Yes, but I don't mean to imply anything more than to describe that there is a break in the quote. I am not suggesting that they have broken it at any particular point for any particular reason.

Senator NELSON. You don't know what the full quote is?

Dr. MCCLEERY. No, sir. I don't know where it came from, where he said it or anything like that.

The bulletin goes on to say that—

> If he [the physician] is a gambling soul—

And again I have to break the quote and make a parenthetical statement. I don't know whether this is a Freudian slip, but constantly the language used here spells soul "s-o-l-e." I assume he means "soul." The quote goes on to say—

> If he is a gambling sole, and almost no physician ever likes to gamble with his patient's welfare. He can prescribe Butazolidin if he is a gambling sole.

Senator NELSON. He can prescribe what?

Dr. MCCLEERY. Butazolidin, a competitive product.

Senator NELSON. That purports to be a quote from whom?

Dr. MCCLEERY. I was quoting from this Bulletin No. 77, September 11, 1967.

Senator NELSON. What about contraindications? The July 12 instructional bulletin says,

> Other than that (pregnancy) the only contraindications to therapy with Indocin are ulcerative colitis, active peptic ulcer, and gastritis.

Now, that isn't a correct statement, is it?

Dr. MCCLEERY. Will you ask that again, please? I don't mean the whole question.

Senator NELSON. In the July 12 instructional bulletin they say,

> Other than that (pregnancy) the only contraindications to therapy with Indocin are ulcerative colitis, active peptic ulcer, and gastritis.

Is that a correct statement?

Dr. MCCLEERY. The statement that you are repeating from the bulletin is an incorrect statement in reference to the full range of contraindications as contained in the package labeling.

Senator NELSON. Since you have inserted the package labeling, that includes the full range of contraindications. Are there several more in addition to these here?

Dr. MCCLEERY. No, sir; there aren't several more. We mentioned one by name in our testimony, and that was that the drug is contraindicated in children. That is not mentioned. There is another inflammatory disease of the intestinal tract which is contained in the package labeling as a contraindication and is somewhat similar to the ones that you were naming, called regional enteritis. That is not on this list. That is the other contraindication.

Senator NELSON. Of course the children—it covers a vast number of people in any event.

Dr. MCCLEERY. Yes, I mentioned it was contraindicated in children.

Senator NELSON. Then the next sentence said,

> These are not unusual signs as you know, Doctor, even aspirin causes some gastric complaints.

Isn't the intent of this sentence to play down the warning of the previous sentence?

Dr. MCCLEERY. I would think so.

Senator NELSON. In Bulletin 84, July 14, 1965, it states:

> Indocin equals or surpasses the effectiveness of Butazolidin.

Is that correct?

Dr. MCCLEERY. If I may, I would like to avoid trying to give a definitive answer to that. The evidence of comparative studies of these two products are unknown to me. I do not know if they exist to an extent that would permit someone to make meaningful comparative claims against another product.

Senator NELSON. Continuing to quote from Bulletin 84, July 14, 1965, and this is the excerpt form the statement: "In therapeutic doses has a safety index comparable to aspirin." Is that correct?

Dr. MCCLEERY. I would have to say that in my understanding of what I feel are the views of people that I have read who work in this field, aspirin, as varied within the dosages used, is really safer. But you are asking me a question, Senator, that I am not really an expert in.

Mr. GORDON. Do you know of any studies which indicate—perhaps you have already answered this—that Indocin equals or surpasses the effectiveness of Butazolidin? On what do they base that statement?

Dr. MCCLEERY. I don't know what they base the statement on, but I must say I am not an expert in the field of these drugs. There are studies I have read, but I am not prepared to make a statement that would be—I am perhaps more reluctant to do it than the statements we are reading were reluctant to make the claims. I know of none that prove this.

Senator NELSON. On page 2 of the bulletin it is stated:

> Lightheadness and dizziness occur occasionally with Indocin as with almost any other medication. For the most part these effects are very mild and very transient.

One of the leading physicians who evaluated Indocin for Merck, Dr. Rothermich, wrote to Merck on June 12, 1963:

> The greatest deterrent to increase in dosage to effective level is the appearance of cerebral toxicity. This manifests itself clinically in excruciatingly severe headaches, dizziness, lightheadedness, disturbance of sensorium, a feeling that

the head is floating away or even separating from the body, and a feeling of detachment from reality.

Does this comment of evaluation by Dr. Rothermich compare with your own claim?

Dr. McCLEERY. The statements that you are reading are opinions of Dr. Rothermich that I haven't seen. They are similar to the kinds of experiences reported with Indocin, and which are included within the package labeling.

Senator NELSON. So they have played down in their instructional bulletin the effects that are described and required in the labeling, is that correct?

Dr. McCLEERY. Well, it seems that they have a dimunition of the impact of the ideas which are being described.

Senator NELSON. On page 3 of the Bulletin No. 66 dated July 7, 1967, we find, you have mentioned this yourself previously:

Indocin should be tried promptly or tried first.

Now, in the AMA's 1967 edition of New Drugs, page 540, we find the following statement:

Present clinical experience indicates that this drug is as effective as the salicylates in patients with rheumatoid arthritis. However, its use is not necessary when salicylate therapy is effective. Although aspirin is still considered the drug of first choice, indomethacin may be tried if aspirin ceases to be beneficial or is no longer tolerated.

Is the statement by the AMA Journal representative of the viewpoint of the FDA?

Dr. McCLEERY. It squares with my own personal understanding of the view of men who are experts and have written on comparative drug trials. In the approved labeling of the drug Indocin, there are no such comparative claims of this sort. It is the kind of view that I was trying to express awhile ago. It is a most common view of the experts in the field that the salicylates are still the drug of first choice to use. They give much of the same benefits that Indocin does if not to all patients.

Senator NELSON. I want to thank you very much, Dr. McCleery. We appreciate your very fine statement and you and your staff associates coming here this morning to testify.

Does anybody have anything they wish to add to the statement?

We will resume hearings, then, again tomorrow morning at 9:30.

Thank you.

(Additional instructions from H. Glassner to All Western District Associates, undated, follow:)

To: All western district associates
From: H. Glassner
Subject: Indocin

The "Indocin" release meeting was great. However, several of you have asked for a concise Product Information Outline from which you can build your own presentation. Here are the "must know" facts on 'Indocin'. Put the words together so they sound like you. Remember, however, no presentation is a good presentation unless it creates prescription specification.

What is Indocin?

Indocin is an entirely new "anti-rheumatic" drug that affords ANTI-INFLAMMATORY ANALGESIC—AND ANTIPYRETIC ACTIVITY. The unique chemical structure of 'Indocin' differs entirely form salicylates, corticosteroids, colchicine and phenylbutazone.

What is Indocin for?

Indocin is effective in the management of both short-term and long-term—acute or chronic inflammatory lesions of the musculoskeletal system including:

Degenerative joint disease of the hip (osteoarthritis);
Gout;
Rheumatoid spondylitis; and
Rheumatoid arthritis.

What will Indocin do?

When inflammation is causing pain and limitation of motion, therapy with 'Indocin' will usually:

Promptly relieve pain;
Reduce fever, swelling, and tenderness; and
Increase joint mobility.

What are the advantages of Indocin?

Indocin is rapid and effective in action. Relief of symptoms is prompt.

(*a*) In most patients with chronic rheumatoid arthritis, 'Indocin usually relieves pain and stiffness within 48 hours.

(*b*) In acute rheumatoid arthritis, or arthritic flares of musculoskeletal pain—'Indocin' usually relieves pain, swelling, and tenderness, and fever within 48 hours.

(*c*) In acute attacks of gout, 'Indocin' is dramatic. Marked reduction of pain is common within two to four hours. Tenderness and heat subside within 24 to 36 hours, and swelling decreases in 3 to 5 days.

In degenerative joint disease—particularly osteoarthritis of the hip—'Indocin' takes a bit longer to work but has clinically provided RELIEF OF PAIN AND INCREASED RANGE OF MOTION.

Indocin has an extended margin of safety

Although 'Indocin' is second in potency only to the steroids—'Indocin' has a wide range of safety.

(*a*) Chemically, 'Indocin' is related to tryptophan, a naturally occurring amino acid. Unlike Butazolidin, it is not an aminopyrine derivative. Therefore, 'Indocin' does not have the well-documented poisonous effects of aminopyrine and related compounds.

(*b*) 'Indocin' has no effect on pituitary or adrenal function. Therefore, the well known and well documented side effects of steroids such as hirsutism, psychic disturbances, etc. are not problems in patients on therapy with 'Indocin'.

Broad applicability

Because 'Indocin' has an extended margin of safety, it can be safely used on any adult patient.

Because 'Indocin' works even in stubborn, long-standing, degenerative joint disease (osteoarthritis of the hip), it undoubtedly will be dramatically, excitingly effective in routine rheumatoid complaints.

What is the dose of Indocin and how it is supplied

(*a*) Indocin is available as a 25 mg. blue & white capsule.

The cardinal rule in dosage with Indocin is start low and go slow.

In chronic arthritides, the starting dose of 'Indocin' is 1 capsule b.i.d. or t.i.d. If response is inadequate, this dose may be increased by 1 capsule daily at weekly intervals. The new dose is continued until adequate response is obtained or until a maximum of 8 capsules per day is reached.

In acute arthritis, the starting dose of 'Indocin' is 1 capsule b.i.d. or t.i.d. If response is inadequate, one additional capsule per day may be added each day until an adequate response is obtained or until a maximum of 8 capsules daily is given.

In acute gout, the recommended dose of 'Indocin' is 2 capsules t.i.d. This dose may be increased to a maximum of 8 capsules per day if necessary.

In chronic gout, 1 capsule b. i. d. may be given with 'Benemid' to minimize the possibility of subsequent attack.

What are the precautions of Indocin therapy?

Unlike Butazolidin, reports of changes in the white blood count in patients on therapy with 'Indocin' have been extremely rare. In most reported cases, it has been impossible to implicate Indocin as the causative agent.

Therefore, unlike Butazolidin, we do not recommend weekly or bi-weekly blood counts in patients being treated with 'Indocin'. Periodic, simple hemoglobin determinations may be made by the physician on routine office visits.

In about six out of ten patients, no adverse reactions of any kind will occur. In about three out of ten patients, very mild transient and tolerable reactions will possibly occur. These reactions would include mild nausea, mild headache, mild dizziness, and the other minor nuisance effects. Usually, these effects will disappear with continued therapy even without dosage adjustment.

In only one out of ten patients were reactions severe enough to justify dosage reduction or discontinuance of therapy.

Learn these facts well enough to handle objections. Then, on every call make sure you leave the physician's office with him completely convinced that—

Whenever, the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling;

When the muscles around an inflamed joint are in spasm causing limitation in motion;

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain musculoskeletal aches and lumbago; or

For short-term use in acute conditions or long-term use in chronic conditions—

Indocin will afford prompt relief to three out of four patients—more effectively—with an extended margin of safety—at less cost—with fever tablets—less dosage adjustment—and, therefore fewer problems to the patient and to his physician than any other currently available agent.

Go get it. This is a big one.

H. GLASSNER.

To: All western district associates.
From: H. Glassner.
Subject: Indocin.

Here is the biggest potential volume product we have released since 'Decadron'. Automatic shipments are in the stores and in the jobbers.

Voluntary, repeat orders are pouring into the Branch. Advise your customers that 12 x 100 'Indocin' are packed in a compact, easy-to-handle shipping carton. This should become the basic unit of sale. Each time you ship a carton of 12 x 100 'Indocin' you put $84.00 more on the bottom line. At 6%, that puts a little better than a brand new $5.00 bill in your pocket.

If you haven't already done so—complete the fourth book of Programmed Instruction. Then, build a detail. Your Field Managers will be testing you on the information contained in Book No. 4.

No matter what else you say, repeat and repeat and repeat this theme until it is indelibly impressed in the physician's mind. Learn it cold. Believe it fervently. Communicate it effectively.

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling.

When the muscles around an inflamed joint are in spasm causing limitation of motion.

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain musculoskeletal aches and stiffness.

For short-term use in acute conditions or long-term use in chronic diseases.

Indocin will afford prompt relief to three of four patients.

More effectively—with an extended margin of safety—at less cost—with fewer tablets—less dosage adjustment—and, therefore fewer problems for both the patient and the physician than any other currently available product.

Let's not make the mistake of trying to teach the physician to diagnose. 'Indocin' is for relief of pain due to inflammation. Let him decide when to use 'Indocin'. However, encourage him to use it early when it will do the patient the most good.

Get hot on this one. We're gonna lead them.

H. GLASSNER.

(The American Law Division opinion previously referred to follows:)

THE LIBRARY OF CONGRESS,
LEGISLATIVE REFERENCE SERVICE,
Washington, D.C., May 7, 1968.

To: Senate Subcommittee on Antitrust and Monopoly (attention Mr. Gordon).
From: American Law Division.
Subject: Does Food and Drug Administration have authority over oral statements of drug manufacturer's representatives who contact physicians directly.

No specific authority is conferred on the Food and Drug Administration to deal with the matter in question. The Food and Drug Act deals, in pertinent part, with labels and labeling. A drug shall be deemed to be misbranded in several situations set forth in the law. See 21 U.S.C. § 352. We have located three court decisions involving prosecutions under the Food and Drug Act for oral representations which apparently were misstatements respecting the product to which they relate. None of these, however, were concerned with statements to physicians. In *U.S.* v. *Hohensee*, 243 F. 2d 367 (1957) the evidence was sufficient to sustain the conviction of the defendant who subsequent to shipment of harmlessly labeled food products in interstate commerce to pre-arranged towns, went to such towns to give lectures and distribute literature promoting the use of such products to promote health. The case of *Nature Food Centres, Inc.* v. *U.S.* 310 F 2d 67 held that defendants selling drugs identified on attached labels as dietary supplements could not meet branding requirements of Federal Food, Drug, and Cosmetic Act through sale of "lecture notes" concerning the drugs where some of the drugs were destined for sale at stores where notes were not available and, even at halls where lectures were delivered and drugs were available, notes were obtainable only upon payment of additional price In *U.S.* v. *Article of Drug, etc.* 362 F. 2d 923 the court held that the evidence supported the finding that the drug company claimant adopted as its own representation a radio broadcaster's claim that vitamins were efficacious for prevention and treatment of human disease, and that claimant intended its products to be used for general purposes recommended by broadcaster, as asserted by the government which charged misbranding in that claimant's catalogs failed to contain adequate directions for use.

These three cases involving oral statements would appear to have but limited application, if any, to the quetsion presented. It seems to us that there is no clearly defined authority for the exercise of control by the Food and Drug Administration over oral statements of manufacturer's representatives to physicians in all situations.

HUGH P. PRICE,
Legislative Attorney.

(Whereupon, at 10:35 a.m., the subcommittee recessed to reconvene at 9:30 a.m., Wednesday, September 18, 1968.)

APPENDIXES

Appendix I

[From Annals of the Rheumatic Diseases, vol. 25, 1966, pp. 334–339]

Indomethacin in In-Patient Treatment of Rheumatoid Arthritis

(By D. A. Pitkeathly, N. R. Banerjee, R. Harris, and J. Sharp, Devonshire Royal Hospital, Buxton)

Indomethacin has been used in the treatment of rheumatic disease for over 3 years. Preliminary reports of the effectiveness of the drug were encouraging (Rothermich, 1963; Norcross, 1963) Katz, Pearson, and Kennedy (1963) also found the drug to be beneficial but treatment had to be discontinued in over 20 per cent of patients because of side-effects. Hart and Boardman (1963) showed that indomethacin produced a measurable reduction in swelling of the proximal interphalangeal joints in patients with rheumatoid arthritis and that, when a placebo and the drug were used alternately, significant rebound effects commonly occurred with the commencement of placebo treatment. Side-effects, principally headache, dizziness, dyspepsia, and mental disturbances, were frequent being observed in over 50 per cent. of patients treated with a dose exceeding 200 mg. A trial of the drug by Wanka, Jones, Wood, and Dixon (1964) showed that indomethacin was effective when compared with a placebo, and a comparative trial against phenylbutazone by Percy, Stephenson, and Thompson (1964) showed that 200 mg. indomethacin was approximately equivalent to 300 mg. phenylbutazone daily, although a decidedly higher incidence of side-effects occurred with indomethacin.

During this period of development of the drug it was supplied in tablet form and the doses used ranged from 150 to 400 mg. daily. Wanka and others (1964), using this preparation and range of dose, reported one case of intestinal haemorrhage and one of perforated gastric ulcer. Lövgren and Allander (1964) used a similar dosage in eighteen patients with rheumatoid arthritis, six of whom had a previous history of peptic ulcer but had negative barium meals immediately before treatment; five patients developed peptic ulcers, two of these having no previous history, and three of the five had severe bleeding.

During the past 2 years indomethacin has been supplied in capsule form and the manufacturers have recommended an initial dose of 50 mg. daily, gradually increasing to a maximum of 150 mg. The incidence of side-effects was stated to have fallen from 50 to 10–30 per cent of all treated patients (Today's Drugs, 1964) as a result of using capsules and more conservative dosage, and Clark (1964) reported satisfactory improvement in many patients of a large group with rheumatoid arthritis using this scale of dosage. Recently Hart and Boardman (1965) have compared 75 mg. indomethacin daily with 300 mg. phenylbutazone daily, in out-patients with rheumatoid arthritis. A double-blind crossover trial was carried out, each drug being given for a period of 28 days. No significant differences were found in the relief of symptoms although there was a greater reduction of morning stiffness with phenylbutazone. There were no significant differences in strength of grip or in improvement in ring sizes of proximal interphalangeal joints, but indomethacin tended to have a greater effect on the latter. The preference of patients was in favour of phenylbutazone. The incidence of side-effects of indomethacin in this short-term trial are not stated, but in long-term studies on patients with rheumatoid arthritis, osteo-arthritis, and ankylosing spondylitis, the authors found that 37 per cent of the patients developed side-effects of drug treatment.

The present study has been carried out to evaluate indomethacin in a dose of 50 to 100 mg. in the in-patient treatment of patients with rheumatoid arthritis. Salicylates are currently the mainstay of drug therapy while the patient is being

treated with rest in bed and splintage followed by graded exercises. It was our aim to decide if indomethacin could effectively replace salicylates under these circumstances.

Hajnal, Sharp, and Popert (1959) have drawn attention to the considerable effect of "spontaneous improvement" in hospitalized patients. In addition to rest in bed and splintage, other features such as increasing familiarity with hospital environment and in the case of strength of grip, practice in the use of the apparatus, contribute to the improvement shown. This must be dissociated from the effect of drug therapy before the value of a new drug can be assessed.

PATIENTS STUDIED AND METHODS EMPLOYED

34 women and eight men with classical and definite rheumatoid arthritis (1958 A.R.A. Criteria—Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) were studied. Before entering the trial each patient spent one week settling into the hospital routine. During this period analgesia was provided by soluble aspirin and was maintained at the pre-admission dose provided that this did not exceed 4 g. daily. If the patient was already on corticosteroids, the dose was maintained at the pre-admission level during the first week and throughout the trial.

Patients were excluded from the study if they had known peptic ulceration or severe dyspepsia or were intolerant of aspirin, or if the grip test could not be adequately performed by reason of severe anatomical deformity of the hands or if the strength of grip exceeded 300 mm. Hg.

The patients were allotted alternately to indomethacin or soluble aspirin on entry. The first drug was given for a 2-week period and then the other drug was administered for a further 2 weeks, so that half the patients received indomethacin followed by soluble aspirin, and the other half received soluble aspirin followed by indomethacin. The soluble aspirin was specially coloured and flavoured and the patients were unaware of the identity of the tablets. It was given in a dose of 4 g. daily throughout the 2-week period. Indomethacin was given in a dose of 25 mg. twice daily for 2 days, followed by 25 mg. three times daily for 6 days and then 25 mg. four times daily for the remaining 6 days.

Of the 42 patients, 38 completed the study. Two patients were withdrawn while taking soluble aspirin, one because of severe deafness and the other on account of repeated vomiting. One patient developed profound dizziness on indomethacin and the drug had to be withdrawn. The fourth patient was given an incorrect dose of indomethacin during the second week of treatment and was therefore excluded from the analysis. Of the remainder, twenty patients had commenced the trial taking soluble aspirin and eighteen patients had started with indomethacin. Five of those starting on solube aspirin were taking prednisolone with a mean daily dose of 9 mg.; seven of those starting on indomethacin were taking prednisolone with a mean daily dose of 10 mg.

Clinical assessment.—Assessments were carried out on the first day of the trial and thereafter at weekly intervals until the completion of the study. As far as possible the patients were assessed at the same time of day throughout and the daily physiotherapy was not given until the assessments had been made. Strength of grip of both hands were recorded weekly. Swelling of the proximal interphalangeal joints was measured using jeweler's rings. These rings were labelled from A to Z with intermediate half-sizes; the diameter of size A was 0.476 in. and the increase in diameter from size A to B was 0.015 in. The patients were questioned concerning headache, dizziness, and dyspepsia, and any other side-effects were noted. At the end of the study the patients' preference for one drug or the other was recorded.

ANAYSIS OF RESULTS

The mean strength of grip at the commencement of the study and at weekly intervals throughout the trial was calculated for each series of patients (Table I).

TABLE I.—MEAN VALUES FOR WEEKLY ESTIMATIONS OF STRENGTH OF GRIP (MM. HG) FOR PATIENTS STARTING ON SOLUBLE ASPIRIN AND INDOMETHACIN

Starting drug	Soluble aspirin	Indomethacin
Number of cases	20	18
Grip (mm. Hg):		
Initial	145.65	159.28
Week 1	[1] 163.90	[2] 194.11
Week 2	[1] 173.60	[2] 194.50
Week 3	[2] 183.80	[1] 199.17
Week 4	[2] 188.30	[1] 202.06

[1] Aspirin.
[2] Indomethacin.

Improvement was most marked during the first week of treatment with both drugs and in this week the average improvement was almost twice as great in those starting on indomethacin as in those starting on soluble aspirin. In the second week the indomethacin group—although then on a slightly higher dosage, having changed from 25 mg. three times daily to 25 mg. four times daily—showed on average no improvement in mean strength of grip but the value in the soluble aspirin group continued to improve, so that after 2 weeks the difference had narrowed considerably. During the second half of the study both groups showed some further average improvement, which was again more steady in those starting on aspirin, who were now on indomethacin; over the whole of the second fortnight those now on soluble aspirin showed only half the improvement of the other group. The total improvement after 4 weeks was virtually identical in the two groups.

* * * * * * *

TABLE IV.—SIDE EFFECTS ATTRIBUTABLE TO SOLUBLE ASPIRIN AND INDOMETHACIN IN 42 PATIENTS

Side effect	Drug	
	Soluble aspirin	Indomethacin
Headache	10	17
Dizziness	3	4
Deafness	6	0
Dyspepsia	10	10
Vomiting	3	1
Diarrhea	3	0
Rash	0	1
Sweating	1	1

* * * * * * *

Patient Preference.—This is shown in Table V. All three patients who were withdrawn from the trial because of severe side-effects on one drug completed 2 weeks of treatment on the other drug and are shown as preferring that drug.

TABLE V.—*Patient Preference*

Preference:	*Number of cases*
For soluble aspirin	21
For indomethacin	13
None	7
Total	41

DISCUSSION

The anti-inflammatory action of indomethacin has been demonstrated convincingly under experimental conditions. Winter, Risley, and Nuss (1963) showed that the drug had a powerful effect in inhibiting granuloma formation in rats. In addition, inflammatory oedema induced by carrageenin was suppressed. Boris and Stevenson (1965) found that indomethacin was the most powerful of a group of five anti-inflammatory agents in inhibiting the inflammatory reaction induced by carrageenin in rats, the others being flufenamic acid, mefenamic acid, oxyphenylbutazone, and phenylbutazone in order of decreasing potency. Under clinical conditions, Hart and Boardman (1963) confirmed this anti-inflammatory action using 150–300 mg. of the drug daily. In view of the high incidence of side-effects with this range of dose we wished to study the effect of indomethacin in a dose not exceeding 100 mg. daily in the in-patient treatment of rheumatoid arthritis and to compare it with soluble aspirin in a dose commonly used in these patients. Studies had already been carried out by Hart and Boardman (1965) and Thompson and Percy (1966) and the drug was found to have considerable therapeutic value in patients with a variety of rheumatic diseases.

In recent years salicylates have been shown convincingly to have anti-inflammatory properties in experimental animals. Spector and Willoughby (1963) showed that systemic sodium salicylate has an inhibitory effect on the volume of exudate in turpentine-induced pleurisy in the rat and causes a non-specific suppression of the action of many substances that increase vascular permeability. Kelemen (1963) studied acute inflammatory oedema in rats using I^{131} serum albumin. He considered that there were two components to the inflammatory response. One was inflammatory swelling which was diminished by salicylate. The other, a possible tissue component, preceded visible swelling, persisted after the oedema had disappeared, and was unaffected by salicylate. In view of this work on salicylates in experimentally-induced inflammation, it must be borne in mind that doses of 4 g. daily in patients with rheumatoid arthritis may have anti-inflammatory activity of the same order of magnitude as that shown by indomethacin in low dosage.

In this study we have used strength of grip and improvement in swelling of the proximal interphalangeal joints measured by jeweller's rings to assess the weekly improvement throughout the trial period. Analysis of mean strength of grip during periods of treatment with soluble aspirin and indomethacin has shown that drug effect was approximately one half of the effect attributable to spontaneous improvement. It has also been shown that indomethacin had a greater effect than aspirin in improving strength of grip and that this difference was just significant at the 5 per cent level. On the other hand, there was no difference between the two drugs in their effect in reducing swelling of the proximal interphalangeal joints and most of the improvement which occurred was the result of spontaneous improvement.

There was a greater preference of patients for soluble aspirin than for indomethacin in this trial. The incidence of headache during soluble aspirin treatment was surprisingly high, so that the patient preference can hardly be due to indomethacin headaches unless these were qualitatively different from the headaches reported during aspirin treatment. Greater pain relief from aspirin in the dosage used may have been important. Hart and Boardman (1963) stated that indomethacin had no analgesic action in the mouse or rat using methods then in use. The manufacturers claim, as a result of controlled clinical studies, that 50 mg. indomethacin is equal in analgesic effect to 600 mg. acetylsalicylic acid. If this is so, then the analgesia produced by aspirin in this study was much greater than that produced by indomethacin.

The high incidence of side-effects of indomethacin reported in the literature has made physicians cautious. Headache and dyspepsia were still fairly frequent in this study despite the low dosage employed and the slow build-up of the drug. On the other hand, the incidence of side-effects except headache differed little from that occurring with 4 g. soluble aspirin daily. There is little doubt that side-effects would have been reported less frequently with both drugs if patients had not been asked about specific symptoms. No serious complications such as gastro intestinal hemorrhage occurred, but the trial was of short duration and patients with severe dyspepsia or known peptic ulcer were not admitted to it. It is to be noted that, in the studies of Hart and Boardman (1965) and Thompson and Percy (1966), cases of neurological disturbance and gastro-intestinal bleeding were reported and that these side-effects could be present after many months of treatment.

SUMMARY

A cross-over trial of indomethacin and soluble aspirin has been conducted in in-patients with rheumatoid arthritis. The indomethacin was increased from 50 to 100 mg. during the treatment period, but the dose of soluble aspirin was maintained at 4 g. daily.

A method of analysis has been used which dissociates drug effect from other factors which may lead to the improvement with time usually observed in hospitalized patients regardless of medication. This has re-emphasized the important contribution of these factors.

Comparison of the two drugs has shown that strength of grip improved to a greater extent during indomethacin treatment and that this result was just significant at the 5 per cent level. Decrease in swelling of proximal interphalangeal joints was very similar during treatment with the two drugs but 21 patients preferred soluble aspirin, whereas thirteen preferred indomethacin, and the remaining seven had no preference.

It is concluded that indomethaci should not replace aspirin in the routine treatment of in-patients with rheumatoid arthritis. However some patients appear to do better with indomethacin and it may therefore be useful in selected cases.

We wish to thank Professor J. H. Kellgren for advice and criticism in the preparation of this paper. Miss F. Bier performed the statistical analysis and we are greatly indebted to her.

REFERENCES

Boris, A., and Stevenson, R. H. (1965). *Arch. int. Pharmacodyn.*, 153, 205.
Clark, G. M. (1964). *Arthr. and Rheum.*, 7, 300.
Hajnal, J., Sharp, J., and Popert, A. J. (1959). *Ann. rheum. Dis.*, 18, 189.
Hart, F. D., and Boardman, P. L. (1963). *Brit. med. J.*, 2, 965.
———, ——— (1965). *Ibid.*, 2, 1281.
Katz, A. M., Pearson, C. M., and Kennedy, J. J. (1963). *Arthr. and Rheum.*, 6, 281.
Kelemen, E. (1963). *In* "Salicylates: An International Symposium sponsored by the Empire Rheumatism Council with the support of the Nicholas Research Institute, Ltd. Post-graduate Medical School of London, 1962", ed. A. StJ. Dixon, B. K. Martin, M. J. H. Smith, and P. H. N. Wood, p. 148. Churchill, London.
Lövgren, O., and Allander, E. (1964). *Brit. med. J.*, 1, 118.
Norcross, B. M. (1963). *Arthr. and Rheum.*, 6, 290.
Percy, J. S., Stephenson, P., and Thompson, M. (1964). *Ann. rheum. Dis.*, 23, 226.
Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A. (1959). *Ibid.*, 18, 49.
Rothermich, N. O. (1963). *Arthr and Rheum.*, 6, 295.
Spector, W. G., and Willoughby, D. A. (1963). *In* "Salicylates: An International Symposium sponsored by The Empire Rheumatism Council with the support of the Nicholas Research Institute Ltd., Post-graduate Medical School of London, 1962", ed. A. St.J. Dixon, B. K. Martin, M. J. H. Smith, and P. H. N. Wood, p. 141. Churchill, London
Thompson, M., and Percy, J. S. (1966). *Brit. med. J.*, 1, 80.
Today's Drugs: Indomethacin (1964). *Ibid.*, 2, 429.
Wanka, J. Jones, L. I. Wood, P. H. N., and Dixon, A. St.J. (1964). *Ann. rheum. Dis.*, 23, 218
Winter, C A., Risley, E. A., and Nuss, G. W. (1963). *Fed. Proc.*, 22, 543.

APPENDIX II

[Reprinted from Annals of Internal Medicine, vol. 49, No. 1, July, 1958, printed in U.S.A.]

RHEUMATOID SPONDYLITIS: MANIFESTATIONS AND MANAGEMENT*

(By Aaron M. Lefkovits, M.D., F.A.C.P., and J. R. Thomas, M.D., Memphis, Tenn.)

Rheumatoid spondylitis is one of the most common arthritic diseases affecting young and middle aged men during their most productive years and, with the exception of trauma, is probably one of the most common causes of backache in this segment of the population. Its importance as a cause of morbidity and disability in young men is attested to by the numerous articles which appeared in the medical literature during the war years and thereafter. However, despite this keen interest, the disease in many patients is unrecognized during its early stages and is allowed to progress until irreversible deformities develop before the correct diagnosis is made and proper management for its control is instituted. It appears, therefore, that some aspects of this disease need further clarification, especially in regard to its earlier recognition and to the institution of proper and effective therapeutic measures.

METHODS

The records of 267 patients in whom the diagnosis of rheumatoid spondylitis was made were carefully reviewed. Some of the available data pertient to this study are indicated in table 1. With few exceptions, all patients were examined and treated by one of us (A. M. L.). Since this study was made at a Veterans Administration hospital, where the majority of patients are males, all these patients were of that sex. The diagnosis of rheumatoid spondylitis in every instance was made on the basis of the history, physical findings and radiographic evidence. Roentgenographic examination included A–P and lateral views of the lumbosacral, dorsal and cervical spines. Whenever indicated, special inclined views of the sacroiliac joints and oblique views of the lumbar and cervical spines were obtained. Blood studies included the following determinations: hemoglobin, white blood cell count, erythrocyte sedimentation rate and, in a few patients, C-reactive protein, total serum proteins, albumin, globulin and A/G ratio. The results are shown in table 2. Treatment consisted of physiotherapy, irradiation of painful areas of the spine, instruction in breathing and postural exercises, measures of rehabilitation, dietetic management, correction of static factors, braces, aspirin, and, in a few patients, hydrocortisone and Butazolidin. During the later period of this study only those patients were treated with irradiation of the spine who failed to respond to the other measures.

TABLE 1.—CLINICAL FEATURES

	Number of patients	Percent
Family history of arthritis	25 of 201	12.4
Trauma	66 of 229	28.8
Subjective complaints of arthritis in peripheral joints	166 of 264	62.8
Objective signs of arthritis in peripheral joints	113 of 266	42.4
Radiographic changes in sacroiliac joints	267 of 267	100.0
Radiographic changes in hip joints	41 of 267	15.3
Calcification of ligaments	89 of 267	33.3
Osteoporosis	64 of 267	23.9

*Received for publication June 4, 1957.

From the General Medicine and Rheumatology Section of the Medical Service, Veterans Administration Hospital, Kennedy Division, Memphis, Tennessee.

Requests for reprints should be addressed to Aaron M. Lefkovits, M.D., Chief, Section on General Medicine and Rheumatology, Veterans Administration Medical Teaching Group Hospital, Park Avenue and Getwell Street, Memphis 15, Tennessee.

TABLE 2.—LABORATORY DATA

	Hemoglobin				White Blood Cell Count			E.S.R. (Wintrobe Method)	
Gm. %	>14.5	>13.5	>10.0	<10.0	>10,000	>5,000	<5,000	>10 per hr.	<10 per hr.
No. of pts	117	70	60	9	57	190	14	209	46
Percent	45.7	27	23.4	3.5	21.8	72.8	5.3	81.9	18

	C-RP		Total Serum Protein		Albumin (Normal 3.0–4.5 gm. %)		Globulin (Normal 2.3–3.6 gm. %)		Reversal A/G Ratio
	Pos.	Neg.	Normal	Abnormal	Normal	Decreased	Normal	Elevated	
No. of pts	23	3	35	0	32	2	25	9	7

OBSERVATIONS

The age of onset (figure 1) of the disease varied from the second to the sixth decade; the youngest patient was 17 years and the oldest 54 years at the onset of the disease. The period of observation (figure 2) varied from a few months to as long as nine years. The greatest number, 153 (57.4%), were in their third decade at the time of onset of the disease (table 3). In 201 patients the presence or absence of arthritic disease in the family was recorded; of these, 25 (12.4%) gave a history of "arthritis" in some other member of the family. Trauma was given as a precipitating factor by 66 (28.8%) of 229 patients. Subjective complaints of peripheral joint involvement were present in 166 of 264 (62.8%); objective signs of peripheral joint involvement in 133 of 266 (42.4%); and sciatic radiation in 63 patients (23.5%). All patients had radiographic evidence of sacroiliac involvement. Calcification of the vertebral ligaments was present in 89 patients (33.3%), and osteoporosis in 64 patients (23.9%). Forty-one patients (15.3%) had hip joint involvement. These data are recorded in table 3, and graphs.

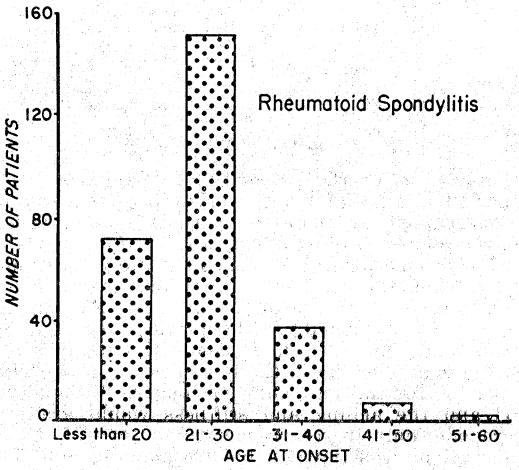

FIG. 1.

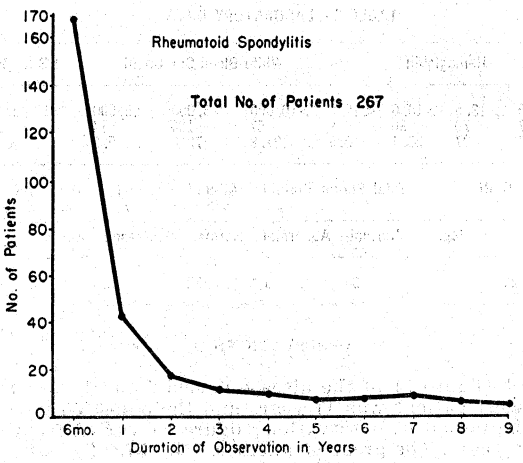

FIG. 2.

TABLE 3.—AGE AT ONSET AND DURATION OF OBSERVATION

Age at onset	Number of patients	Duration of observation	Number of patients
Less than 20	71	Less than 6 months	168
		More than 1 year	41
21 to 30	152	More than 2 years	17
		More than 3 years	11
31 to 40	37	More than 4 years	10
		More than 5 years	4
41 to 50	6	More than 6 years	5
		More than 7 years	6
51 to 60	1	More than 8 years	2
		More than 9 years	3
Total number of patients	267		267

MODE OF ONSET

The onset of the disease in the majority of the patients was insidious, generally over a period of several months or even years, and progression of the disease was interrupted by pain-free periods lasting several weeks or months. With each relapse, however, the symptoms were generally more severe and the duration of each episode was longer; ultimately the symptoms became more or less constant. Thus, there was a gradual increase in the severity of the patient's complaints. In a small number of patients the course of the disease was progressive and developed fairly rapidly, although they continued to have periods of exacerbations and remissions. The most common symptoms at the onset of the disease were stiffness and aching in the low back in the morning on awakening which would persist for half an hour or longer. With activity, the back would "limber up" and the aching and stiffness would gradually disappear toward the late forenoon, only to return toward the end of the day or during the night while the patient was lying in bed, awakening him. The severity of the backache varied considerably in different patients. Characteristically, it awakened the patient two or three hours after falling asleep. The patient would then get off the bed and walk about for one-half hour or longer to obtain relief; then he would return to bed, only to be awakened again in two or three hours, to repeat the process of walking to obtain relief. Patients whose disease was more severe repeated this process two to three times nightly, so that their rest and sleep were markedly disturbed and, as a result, their general well-being suffered, their appetites became poor, and they lost weight. In some patients numbness of the lower extremities accompanied the aching and stiffness in the low back, and they "had to rub" their lower extremities to obtain relief.

In many patients the disease began as "catches, like pinching of a nerve" in one or the other hip region, at times radiating anteriorly to the iliac crests or abdomen. A few patients complained of weakness, or a sensation of "giving way" of the hip, alternating from one to the other hip. Radiation of pain to the buttocks, groins or along the posterior or, less often, the lateral aspect of the lower extremities to the knees or ankles occurred in some patients and, in a few, tingling in the toes on walking. In some, the backache was aggravated on coughing, sneezing, lifting weights or on any movement of the spine. The aching in the back at times was so severe that it seemed to "double up" the patient. A few subjects stated that the backache was accompanied by a tightness or "knot" in the abdomen, spasmodic contractions and rigidity of the abdominal musculature. Patients with involvement of the dorsal spine complained or soreness or migratory sharp pains in the chest during respiration and yawning, and had varying degrees of impaired chest expansion. The complaints were generally worse after periods of inactivity and, in some patients, during inclement weather. A few patients dated the onset of aching and stiffness in the low back to a time when they were treated in a hospital for some other apparently unrelated disease, such as gunshot wound, tonsillitis, etc. Three patients had been explored surgically for herniation of the nucleus pulposus at other institutions prior to our observation. A small number of patients had been believed to be psychoneurotic before the nature of their complaints was recognized, the correct diagnosis made and proper therapy instituted. In contrast, a few patients had only minor complaints referable to the spine, despite well developed deformities and advanced radiographic changes. These patients were generally older men in whom the disease was accidentlly discovered while they were in the hospital for the treatment of an unrelated conditon, such as hypertension, coronary artery disease, pulmonary emphysema, etc. Careful questioning of these pateints revealed that in the past they had had only temporary discomfort in the back, consisting of aching and stiffness which did not interfere with the pursuit of their occupation or customary activities.

PHYSICAL FINDINGS

There was considerable variation in the objective findings. In the milder cases, during the early stages of the disease, no abnormal physical findings were noted and, as a rule, no abnormalities were seen on the radiograms. These were diagnosed on subsequent admissions to the hospital when definite objective abnormalities were found and radiographic evidence of the disease developed. In these instances we found the various leg and spinal maneuvers, particularly Lasègue's, Patrick's Gaenslen's and Ely's, and extent of chest expansion, of great help in arriving at the correct diagnosis.[1] Patients in whom the disease was more advanced presented some or all of the following manifestations in different degrees of severity: flattening of the lumbar spine, with partial or complete obliteration of the normal lumbar lordotic curve and exaggeration of dorsal kyphosis; flattening of the chest and impaired chest expansion; tenderness on pressure or percussion over the sacro-iliac joints and vertebral column; varying degrees of atrophy of the muscles of the spine; rigidity and impairment of some or all spinal movements; anterior fixation of the cervical spine; forward crouching deformity of the entire vertebral column, the so-called "poker spine"; and "en masse" movement of the entire spine. One patient had such marked anterior flexion and rigidity of the vertebral column that the longitudinal axis of the head was parallel to the floor. Several patients who had involvement of the hip joints had a characteristic waddling gait, walking with slightly flexed knees, forward-bent body and hyperextended neck, the upper extremities swinging in a plane posterior to that of the body as they shifted the pelvis from side to side with each step.

[1] Lasègue's Maneuver: Flexing the extended lower extremity upon the abdomen and noting the angle of flexion at which the pain in the low back is reproduced.
Patrick's Maneuver: With the patient in the supine position, the leg and thigh are flexed and the lower extremity is abducted and externally rotated at the hip.
Gaenslen's Maneuver: Hyperextension at the hip of the extended lower extremity while the opposite lower extremity is forcibly held by the patient in the knee-chest position.
Ely's Maneuver: With the patient in the prone position, the leg is flexed on the thigh and the lower extremity is hyperextended at the hip.
Chest Expansion: The circumference of the chest is measured at the level of the nipples at the end of full inspiration and expiration.

LABORATORY DATA

Nine patients (3.5%) had less than 10 gm. % hemoglobin; 130 patients (52%) had mild to moderate decrease of hemoglobin concentration, and 117 patients (45%) had normal levels of hemoglobin. The white blood count was more than 10,000 per mm.^{3} in 57 patients (21.8%); the highest count was 16,400; 14 patients (5.3%) had counts of less than 5,000 per mm.^{3}; the lowest count was 3,200; 190 patients (72.8%) had normal white cell counts. The erythrocyte sedimentation rate was normal in 46 (18%) and abnormally elevated in 209 patients (81.9%); the highest level was 54 mm. in one hour. The C-reactive protein was determined in 26 patients; it was positive in 23 (88.4%) and negative in three patients. The total serum protein level was normal in all 35 patients in whom it was determined. The levels of the albumin and globulin fractions were determined in 34 patients. The level of albumin was normal in 32 and below normal in two patients; the globulin fraction was normal in 25 and abnormally elevated in nine patients; the highest level of globulin was 4.9 gm.%. The albumin-globulin ratio was reversed in seven patients (table 2).

RADIOGRAPHIC CHANGES

It is generally known that the subjective manifestations of rheumatoid spondylitis may make their appearance long before definite evidences of the disease are seen in the radiograms of the sacro-iliac joints and/or of the spine. This interval may vary from a few months to a few years. A still greater difficulty is the recognition and correct interpretation of the early radiographic changes caused by the disease in the sacro-iliac joints, and particularly in the small diarthroidal joints of the vertebral column, namely, the apophyseal, the costovertebral and costrotransverse articulations. The differentiation of these minor changes from the normally occurring variations in the size, shape and direction of the articular facets is extremely difficult. We have obtained considerable help from inclined views of the sacro-iliac joints taken with the x-ray tube tilted at an angle of approximately 35°, and oblique views of the lumbar and cervical spines. The inclined views of the sacro-iliac joints render clearer visualization of their margins and joint spaces, so that minor changes could be differentiated more readily from the normally occurring variations.

All patients had radiographic evidence of involvement of the sacro-iliac joints. These changes were varied: narrowing or widening of the joint spaces, irregular and indistinct joint margins, at times serrated edges, partial or complete obliteration of the joint spaces, spotty osteoporosis and irregular sclerosis of the adjacent sacrum and/or ilium. Similar abnormalities were noted in the apophyseal joints of the lumbar spine and the cervical spine. Adequate or correct recognition of such changes in the dorsal spine was rarely possible because of interference by overlapping rib shadows. Calcification of spinal ligaments was recognized in 89 patients (33.3%). The degree and extent of calcification also varied markedly; in some, it was present only in two or three isolated areas of the spine irregularly spaced; in others, it involved all the ligaments, produced the characteristic "bamboo effect," and transformed the entire spine into a rigid column. The hip joints were involved in 41 patients (15.3%); the abnormalities consisted of varying degrees of narrowing of the joint spaces, erosions of the cortices of the head of the femur and acetabulum, spotty osteoporosis, and irregular areas of sclerosis in the head of the femur and acetabulum.

In a few patients the margins of the symphysis pubis showed considerable irregularity and spotty osteoporosis of the adjacent bones. Irregularities of the lower margins of the ischia, spotty sclerosis and osteoporosis of the adjacent bones were also occasionally present. Osteoporosis of the entire spine was noted in 64 patients (23.9%).

TABLE 4.—RESPONSE TO THERAPY

	Number of patients	Response				Percent good or excellent
		None	Fair	Good	Excellent	
Physiotherapy	95	4	21	52	18	73.7
Radiation:						
1 course	116	13	17	57	29	[1] 74.1
2 courses	42	1	8	23	10	[1] 78.5
3 courses	7	0	1	3	3	[1] 85.7
Total	260	18	47	135	60	75.0

[1] Mean, 75.5 percent.

ASSOCIATED AND INTERESTING MANIFESTATIONS

Three patients presented the triad of Reiter's syndrome, i.e., urethritis, iritis and arthritis involving both the spine and some of the peripheral joints. One patient had complete ankylosis of the temporomandibular joints and was unable to separate his jaws sufficiently to permit the intake of solid food. The condyles of the mandible were resected. Ankylosis recurred several months later; it was then relieved by arthrotomy and replacement of the condyles by Vitallium prostheses. Thirteen patients (4.5%) had iritis or iridocyclitis; six of these had involvement of the peripheral joints also. Five patients (1.8%) had psoriasis; all had involvement of the peripheral joints also. Thirty-six (13.5%) had various forms of anomalies of the spinal column; these are indicated in table 5.

DIAGNOSIS

Rheumatoid spondylitis is easily recognized in patients in whom the disease is well developed. During its early stages, however, the diagnosis is often difficult. When objective manifestations of the disease, or corroborative radiographic changes, are lacking, the fatigability, weight loss and inconstant pain in joints or muscles of the spine are usually ascribed to psychogenic factors. Since there are no specific diagnostic tests, it is often impossible to arrive at the correct diagnosis until characteristic signs of the disease or abnormal radiographic changes appear. We found the following of considerable value in diagnosing the disease: (1) aching in any part of the back in a young man which occurred often during the night and induced him to get off the bed to "limber up"; (2) careful evaluation of results of leg and spinal maneuvers, and particularly the flexibility or rigidity of the spine on body movements; (3) meticulous examination of x-rays of the sacro-iliac joints, and especially of the inclined views of these joints. The laboratory data were of limited value in diagnosing the disease. The erythrocyte sedimentation rate and C-reactive protein were elevated in the majority of patients. The hemoglobin level was slightly to moderately decreased in approximately half of the patients.

TABLE 5.—*Associated and interesting manifestations*

Reiter's syndrome	3
Iritis	13
Psoriasis	5
Anomalies of vertebral column:	
Transitional lumbosacral joint	15
Spina bifida occulta	8
Spondylolysis	6
Spondylolisthesis	3
Miscellaneous	4

MANAGEMENT

Seven patients were asymptomatic at the time of observation and needed no therapy. The remaining 260 patients were treated with a variety of therapeutic measures. The complaints and findings of each patient were carefully considered prior to outlining his therapeutic regimen. Boards were placed under the mattress to prevent sagging of the bed, and the patient was advised to use no pillow under his head while lying in the supine position. Pillows were used until the head when the patient was lying on his side; they were also used until the lumbodorsal spine while lying in the supine position, or at some level under the trunk while lying in the prone position, provided such positioning of the pillow added to his comfort. Static factors such as tilting of the pelvis, inequalities in the length of the lower extremities or weak feet were corrected by construction of heel lifts, metatarsal bars, arch supports, etc. Dental care was given. Instruction in deep breathing and in exercise to correct postural abnormalities and to strengthen the muscles of the back and abdominal wall was given. Appropriate dietetic management was prescribed, i.e., patients who were underweight were given a high calorie and high protein diet (approximately 3,000 calories containing 100 to 150 gm. of protein daily), and overweight patients were placed on a reducing diet (800 to 1,200 calories). Dry or moist heat (infrared, diathermy, hydrocollator pack) was applied locally to the painful regions of the spine and to the involved peripheral joints. Ultrasound was applied in some instances. Occupational and corrective therapy was employed. When present, synovial fluid was aspirated in peripheral

joints, and hydrocortisone, 25 to 50 mg., was injected intra-articularly whenever this was deemed advisable. Aspirin, 0.3 to 1 gm. at four-hour or longer intervals, was used to control pain whenever needed. A few patients who complained of severe pains in the chest and abdomen of radicular distribution, or had spasm of the abdominal and intercostal muscles, were given hydrocortisone orally (50 to 100 mg. daily in divided doses), or phenylbutazone (400 to 600 mg. daily) for short periods of time. Radiation therapy [2] was administered with the Maximar 250 Kv or the Picker 200 Kv unit to painful areas of the spine through one to five portals in doses of 150 to 200 r as measured on the skin or air on alternate days for a total dose of 600 to 750 r to each area. The size of the portals over the sacro-iliac joints was 10 by 12 cm., and over the spine, 6 by 12 to 6 by 15 cm. The following factors were employed:

Filter—Thoreaus No. 2 or 0.5 mm. Cu and 1 mm. Al.

HVL—1 or 2 mm. of Cu.

If symptoms persisted, a second course of radiation therapy consisting of 450 to 600 r through each of two to five portals was given at an interval varying from six weeks to several months. A few patients were given a third series, several months later, consisting of 300 to 450 r through each of one to three portals. No serious toxic reactions were observed from irradiation. A number of patients complained of nausea and occasional vomiting, and a few had a moderate degree of leukopenia. The leukopenia was temporary. The nausea and vomiting were relieved by Dramamine in doses of 50 mg., or Bonamine in 25 mg. doses.

Most patients whose radiograms showed osteoporosis were placed on a so-called "osteoporotic regimen" for a period of three weeks. This regimen consisted of the following: (1) high calorie, high protein diet; (2) ascorbic acid, 100 mg. orally, daily; (3) depo-testosterone, 25 mg. intramuscularly, three times weekly; (4) stilbestrol, 1 mg. orally, daily; (5) vitamin B_{12}, 100 μg intramuscularly, three times weekly. Sixty-three patients were fitted with braces (Taylor, three-point, Knight or von Wersowitz) to support the lumbodorsal spine. Plaster body casts with wedging or turn-buckles were employed in a few patients in an attempt to correct extreme forward-crouching deformities. Three patients had arthrodesis or arthroplasty of one or both hip joints. One patient had bilateral arthroplasty of the temporomandibular joints to relieve ankylosis of these joints, and one patient had arthrotomy and synovectomy of the left sternoclavicular articulation.

The nature of the disease in the light of presently held views was explained to the patient, with assurance of its generally benign character and eventual "burning out" of activity. The patient was encouraged to maintain an optimistic outlook. Emphasis was placed on the importance of maintaining good posture to prevent the development of deformities, of continuing muscle strengthening and breathing exercises, of the use of physiotherapeutic measures at home, and of the necessity of avoiding overexertion and upper respiratory tract or other infections. He was also advised to shift his position at sufficiently frequent intervals to prevent too great a "jellying" effect, to avoid bending over or lifting heavy objects, to bend his knees as in stooping, instead of bending his spine, when lifting objects off the floor, tying shoelaces, etc., and to avoid postures or activities that aggravated his discomforts. An attempt, not always successful, to rehabilitate the more severely affected patients was made by giving them vocational guidance and assistance in changing to an occupation which did not involve standing or sitting for prolonged periods, or arduous physical exertion.

RESULTS

It was difficult to evaluate the results of therapy correctly in terms of arrest of the disease, or the extent of relief of the subjective complaints. Duration of hospitalization could not be used as an indicator because many of our patients remained in the hospital for reasons other than their complaints referable to the spine. In estimating the effect of therapy, we relied generally on the degree of lessening of subjective complaints, especially decrease or disappearance of aching and stiffness, and extent of freedom of body movements. The degree of improvement was expressed as: (1) excellent: complete relief of subjective complaints and ability to resume regular occupation; (2) good: considerable relief of subjective complaints and ability to carry out body movements with relative freedom; (3) fair: some decrease of aching and stiffness; (4) no effect. The results are indicated in table 4.

[2] Radiotherapy was administered under the supervision of Dr. Ralph Braund, Dr. Walter Mendel and Dr. Benjamin Greenberg.

It is seen that "good" or "excellent" response was noted in 70 of 95 patients (73.7%) who were not given irradiation therapy, and in 125 of 165 patients (75.7%) who were given one to three courses of irradiation. There is therefore no significant difference between the two groups. We must emphasize, however, that the comparison is not valid because: (1) irradiation was only one of several therapeutic measures employed in the management of our patients, and (2) we did not evaluate separately the efficacy of physiotherapeutic measures apart from irradiation therapy. Our aim was to employ a therapeutic regimen which would expeditiously bring about a satisfactory remission of the disease and maintain this remission as long as possible.

DISCUSSION

During the course of this study we were impressed by the variability of the subjective manifestations and the general lack of correlation between subjective complaints, clinical manifestations, alleged disability and the roentgen manifestations, especially during the early stages of the disease. We became aware of the influence of the expected gain to be derived from the persistence of complaints in regard to awards of disability compensation in many of our veteran patients. Nevertheless, the diagnosis could be made with certainty in most of these patients. We found the following clinical features to be of value in diagnosing the disease during the early stages: (1) the complaint of aching and stiffness in any part of the lumbodorsal spine, occurring during the night, awakening the patient two to three hours after he had fallen asleep, and necessitating his getting off the bed and walking around in order to "limber up" and obtain relief; (2) the repetition of this process two to three times nightly; (3) the occurrence of stiffness and aching in any part of the lumbodorsal spine on awakening in the morning, but "limbering up" upon resumption of activity; (4) reaction of the patient to the performance of the various orthopedic maneuvers.

We were also impressed by the difficulty in correctly interpreting the earliest radiographic changes and their differentiation from the normally occurring variations in the margins of the sacro-iliac and apophyseal joints. We also became aware of the difficulties in estimating the extent of relief obtained separately from physiotherapy and from irradiation. This difficulty was partly due to the fact that the relief of subjective complaints occurred not infrequently two to four weeks after completion of irradiation therapy. In our experience, the best results were generally obtained from the combination of physiotherapy, irradiation, postural and muscle exercises, the judicious use of aspirin and correction of static factors and of established deformities by orthopedic procedures.

SUMMARY

The clinical features and roentgenographic signs in 267 patients with rheumatoid spondylitis are described. The difficulties in diagnosis encountered during the early stages of the disease are discussed, and methods found helpful by the authors in diagnosing the disease during its early stages are described. Management of the disease is discussed, and results of therapy in this series of cases are tabulated.

SUMMARIO IN INTERLINGUA

Es describite manifestationes clinic e le constatationes roentgenographic in 267 patientes mascule con spondylitis rheumatoide. Le diagnose e le tractamento es discutite. Le etates del patientes al tempore del declaration del morbo variava inter le secunde e le sexte decennio. A judicar per le gravamines subjective del patientes, affection de articulation peripheric esseva presente in 166 ex 264 casos (i.e. 62,8%). Signos objective de affection de articulation peripheric esseva presente in 113 ex 266 casos (i.e. 42,4%). In le majoritate del casos, le declaration del morbo esseva insidiose. Le grados de severitate del dolor dorsal variava considerabilemente in differente patientes. In 63 casos (i.e. 23,5%) illo esseva accompaniate de radiation sciatic e de paresthesias. In le casos characteristic, le patientes esseva eveliate perdolores dorsal duo a tres horas post addormir se. Alicunes habeva dolorose contractiones del musculos abdominal e acute dolores migratori in le thorace durante le respiration.

Le constatationes physic variava grandemente in differente patientes. Observationes frequente esseva applatation del thorace e del spina lumbar, oblitteration del curva lordotic, exaggeration de cyphosis dorsal, dysfunction del expansion del thorace, rigiditate con movimento "como massa unite" del spina integre, e dys-

function del movimentos spinal. Le niveleo de hemoglobina esseva infra le norma in 55% del patientes. Le numeration leucocytic esseva normal in 72,8%. Le sedimentation erythrocytic esseva anormalmente accelerate in 209 casos (i.e. 81.9%). Vistas oblique del articulationes sacro-iliac facilitava grandemente le recognition de precoce alterationes radiographic causate per le morbo. Le alterationes radiographic in le articulationes sacro-iliac e apophysee consisteva de restriction o allargation del spatios articular, de irregular o pauco distincte margines articular, e de oblitteration partial o complete del atriculationes. Evidentia radiographic de affection sacro-iliac esseva trovate in omne le casos. Calicification de ligamentos vertebral esseva presente in 89 casos (i.e. 33.3%), osteoporosis in 64 (i.e. 23.9%).

Tres patientes exhibiva le triade del syndrome de Reiter. Un patiente habeva ankylosis complete de ambe articulationes temporamendibular. Dece-tres (i.e. 4.5%) habeva iritis o iridocyclitis. Cinque habeva psoriasis. E. 36 (i.e. 13.5%) habeva anormalitates del columna vertebral.

Le tractamento utilisava varie mesuras therapeutic. Factores static esseva corrigite. Le patientes esseva instruite in como respirar e como executar exercitios postular. Un appropriate regime dietetic esseva prescribite. Calor humide o siclesseva applicate al region dolorose del columna vertebral e del afficite articulationes peripheric. Fluido synoviad esseva aspirate ab le articulationes peripheric. Hydrocortisona (25 a 50 mg) esseva injicite in le articulationes. Esseva utilisate therapia occupational e corrective. Aspirin (0,3 a 1 g) esseva administrate pro subjugar le dolores. Alicunes del patientes recipeva diurnemente doses oral de hydrocortisona (50 a 100 mg) o de phenylbutazona (400 a 600 mg). Patientes con osteoporosis recipeva regimes osteoporotic. Sexanta-tres esseva equipate con apparatos orthopedic. Cento sexanta e cinque recipeva inter un e tres cursos de roentgenotherapia profunde per inter un e cinque portales dirigite a areas dolorose del columna vertebral. Esseva administrate 600 a 750 r a omne portal in le prime curso, 450 a 600 in le secunde curso, e 300 a 450 r in le tertie curso. Cento vinti-cinque (i.e. 75,7%) obteneva bon o excellente responsas ab le irradiation. Le melior resultatos esseva effectuate per le combination de physiotherapia, irradiation, exercitios postural emuscular, uso judiciose de aspirina, e correction de factores static e de establite deformitates per mesuras orthopedic.

BIBLIOGRAPHY

1. Boland, E. W., and Present, A. J.: Rheumatoid spondylitis, J. A. M. A. 129: 843, 1945.
2. Hench, P. S., Slocumb, C. H., and Polley, H. F.: Rheumatoid spondylitis. Questions and answers, M. Clin. North America 31: 879, 1947.
3. Hart, D. F., Bagdanovitch, A., and Nichol, W. D.: The thorax in ankylosing spondylitis, Ann. Rheum. Dis. 9: 116, 1950.
4. Baker, L. D.: The diagnosis and care of Marie-Strümpell arthritis, Postgrad. Med. 15: 428, 1954.
5. Toone, E. S., Jr.: The treatment of rheumatoid spondylitis, Am. Pract. 2: 530, 1948.
6. Polley, H. F., and Slocumb, C. H.: Rheumatoid spondylitis: a study of 1,035 cases, Ann. Int. Med. 26: 240, 1947.
7. Mowbray, R., Latner, A. L., and Middlemiss, J. H.: Ankylosing spondylitis, Quart J. Med. 18: 187, 1949.
8. Hart, F. D., Robinson, K. C., Allchin, F. M., and Maclagan, N. F.: Ankylosing spondylitis, Quart J. Med. 18: 217, 1949.
9. Rolleston, G. L.: The early radiological diagnosis of ankylosing spondylitis, Brit. J. Radiol. 20: 288, 1947.
10. Oppenheimer, A.: The apophyseal intervertebral articulations roentgenologically considered, Radiology 30: 724, 1938.
11. Borak, J.: Significance of the sacroiliac findings in Marie-Strümpell spondylitis, Radiology 47: 128, 1946.
12. Golden, R.: Diagnositic roentgenology, 1956, The Williams and Wilkins Co., Baltimore, p. 543.
13. Boland, E. W., and Shebesta, E. M.: Rheumatoid spondylitis, correlation of clinical and roentgenological features, Radiology 47: 551, 1946.
14. Guest, C. M., and Jacobson, H. G.: Pelvic and extrapelvic osteopathy in rheumatoid spondylitis, Am. J. Roentgenol. 65: 760, 1951.

APPENDIX III

SCHERING CORP.,
November 3, 1967.

HON. GAYLORD NELSON,
U.S. Senate,
Washington, D.C.

DEAR SENATOR NELSON: In the course of the July 24, 1967, hearings before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, you referred to the "research . . . done by the National Institutes of Health with prednisone," and interrogated Mr. W. H. Conzen, President of Schering Corporation, concerning the report you had received from the NIH as to its expenditures in that regard.

You stated that you had been informed by NIH that they spent a total of $2,114,000 in intramural research on prednisone and prednisolone in the years 1953 through 1967, and that, in addition, NIH had submitted to you a record of expenditures totaling $14,384,144 in extramural research grant obligations for the period from 1953 through 1967.

You further stated (Transcript, p. 1032): "This involved 639 grants from the period 1953 through 1967. These grants were not, I understand, exclusively to do research in prednisone and prednisolone, but in each of these 639 grants, research was done on prednisone and prednisolone, and that totaled $14,384,144."

You asked that the listing of the intramural research expenditures and the table of the extramural research obligations be printed at the conclusion of Mr. Conzen's testimony. The interpretation given to these statements by the press throughout the country is typified by the following:

"Senator Nelson of Wisconsin pointed out that some 60 million dollars had been spent on prednisone research and development grants by the National Institutes of Health. So much for the claim that in this instance private industry carried the ball" (*Times Herald*, Carroll, Iowa).

"Nelson also took issue with Schering's claim of its contributions as the discoverer and developer of prednisone. He cited figures that the National Institutes of Health has spent some $60 million in development and research grants on the drug" (The Washington Post, Washington, D.C.).

To clarify this matter, our Research Vice President requested NIH to furnish us information on this subject. We are now in receipt of its response, a copy of which we are enclosing. We ask that it, together with this communication, be incorporated into the record of the proceedings so that the latter may be more precise and complete.

Very truly yours,

IRVING H. JUROW,
Vice President and General Counsel.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
NATIONAL INSTITUTES OF HEALTH,
Bethesda, Md., October 4, 1967.

DEAR DR. GIBSON: This is in response to your recent inquiries concerning references made to NIH support of research on prednisone and prednisolone before the Senate Select Committee on Small Business Subcommittee on Monopoly, chaired by Senator Gaylord Nelson. We are enclosing a copy of the material supplied to the Committee in response to their request.

There are several points which need to be reemphasized, although they were fully explained by Senator Nelson during the hearing on July 24. As you will see in the attached document, the research reported (both intramural and extramural) covered prednisone and prednisolone for the fiscal years 1953 through 1967. The intramural funds reported were spent entirely on prednisone or prednisolone research. The footnote on the extramural research data (which was read into the hearing record by Senator Nelson, according to a member of his staff) reads as follows:

> "Extramural obligations overestimate funds devoted to prednisone and prednisolone since all grants in which prednisone and/or prednisolone were named were counted in the total."

As far as the method of compiling the information is concerned, the Division of Research Grants, together with the Science Information Exchange, conducted a hand search of research projects either through the "Notice of Research Project" or through the Public Health Service Index for fiscal years 1953–1965.

A punch card run produced the data for FY 1966 and 1967. Projects included here are ones for which prednisone or prednisolone played a sufficiently prominent role to be included in the summary research protocol. We felt that we had no basis for attempting to prorate the amount of the grant award among its various elements. Therefore, we chose to explain the limitations of the data in the above-quoted footnote.

Your inquiries raise several other matters which are of some concern to us. The first is the matter of the misquoting of Senator Nelson in the *Washington Post* on July 25. We regret that our response to the Senate Committee has become embroiled in this controversy, but we are certain that you were not intending to involve or blame the NIH in any way for the error of the *Washington Post* or the fact that this error was picked up by other newspapers.

A second matter of concern to us was the statement in your letter of August 14:

> "I particularly would question the purpose of the large sums expended in recent years after the activity of the drugs in question had been quite thoroughly explored by many laboratories throughout the world."

A review of our Research Grant Indexes indicates a shift of emphasis in recent years in projects involving these agents from subjects primarily within the purview of the National Institute of Arthritis and Metabolic Diseases or the National Institute of Allergy and Infectious Diseases to those more within the purview of the National Cancer Institute. This corresponds to our experience in our own intramural program as well, with the National Cancer Institute being the only Institute with increasing in-house research in recent years directly related to prednisone and prednisolone. We believe that this shift of emphasis may account for the level of expenditure which you questioned.

We welcome this opportunity to clarify our position with respect to this matter, and hope the attached information will meet your needs.

Sincerely yours,

JAMES A. SHANNON, M.D.
Director.

ESTIMATED NIH RESEARCH EXPENDITURES FOR DIRECT OPERATIONS [1] [2] RELATED TO PREDNISONE AND PREDNISOLONE, FISCAL YEARS 1953–56

Fiscal year	NCI	NIAMD	NINDB
1953	0	$15,000	0
1954	0	50,000	$18,000
1955	0	40,000	18,000
1956	$10,000	30,000	10,000
1957	57,000	20,000	10,000
1958	13,000	10,000	0
1959	74,000	10,000	0
1960	19,000	0	0
1961	29,000	0	0
1962	11,000	0	0
1963	84,000	0	0
1964	231,000	0	0
1965	394,000	0	0
1966	409,000	0	0
1967	552,000	0	0
Total	1,883,000	175,000	56,000
Total NIH [3]		2,114,000	

[1] Include contracts.
[2] Funds spent for purchase of drugs for the treatment of NIH Clinical Center patients not included.
[3] NIAID, none.

NIH EXTRAMURAL RESEARCH GRANT OBLIGATIONS, FISCAL YEARS 1953–67 [1]

Fiscal year	Total funds	Number of grants
1953	$156,237	12
1954	327,711	12
1955	394,817	18
1956	350,554	15
1957	326,554	21
1958	655,725	37
1959	783,502	44
1960	930,866	52
1961	1,134,729	56
1962	1,229,653	68
1963	1,338,872	60
1964	1,384,401	60
1965	1,683,464	69
1966	1,695,827	61
1967	1,991,232	[2] 54
Total	14,384,144	639

[1] Extramural obligations overestimate funds devoted to prednisone and prednisolone since all grants in which prednisone and/or prednisolone were named were counted in the total.
for fiscal year 1967.
[2] Incomplete data.

Note: Total intramural and extramural, $16,498,144.

○