Reports have been published of the successful treatment with ampicillin of a carrier of *Salm. typhi*, but of failure in six carriers of *Salm. typhimurium* (Stewart *et al.*, 1961 ; Trafford *et al.*, 1962). Ampicillin has failed in three carriers of salmonellae, but a fourth patient remained negative one month after cholecystectomy and ampicillin therapy (Tynes and Utz, 1962). The five relapses in the present series of 10 patients may have been due to the use of an inadequate dose, as they all occurred after treatment with less than 1 g. six-hourly. The administration of a larger dose in two of them resulted in a clinical and bacteriological cure. It has been suggested that ampicillin may not reach the lower ileum in a concentration inhibitory to pathogenic bacteria, owing to rapid absorption from the upper part of the small intestine, and possibly to local destruction by penicillinase (Stewart and Harrison, 1961). This may contribute to failure of the drug in acute salmonelloses.

Chronic salmonella infections are notoriously difficult to treat (Main, 1961). In acute salmonelloses chloramphenicol is unsatisfactory in preventing the development of the carrier state (Douglas, 1950 ; Good and Mackenzie, 1950 ; Woodward *et al.*, 1950). This is due to the bacteriostatic action of chloramphenicol and the low concentrations achieved in bile. Ampicillin, being bactericidal and highly concentrated in bile, may be a useful drug in carrier states when given in an adequate dose of at least 1 g. six-hourly for 21 days. It probably represents no advance in the treatment of acute salmonelloses, although more extensive trials are necessary (*Brit. med. J.*, 1961). At the time of writing there was a large epidemic of paratyphoid infection in the Edinburgh area and ampicillin treatment was being compared with chloramphenicol for both the acute infection and the carrier state in over 130 patients. It is hoped to publish the results of this trial after adequate long-term follow-up studies have been completed.

Side-effects similar to those seen with other penicillins occurred in seven (19%) of the patients but were readily reversible. It seems likely that cross-sensitization exists among all penicillins, and it is important that patients should be questioned about previous penicillin allergy before ampicillin or any other penicillin is given.

Summary

Forty-eight patients were treated with ampicillin, 37 suffering from infections of the urinary tract, 10 from salmonelloses, and one from *Kl. pneumoniae* septicaemia. The ampicillin sensitivity of the causative organisms has been studied, and concentrations of ampicillin in blood and urine have been estimated. In the treatment of infections of the urinary tract ampicillin should be reserved for infections due to *Proteus* spp. It is not the drug of first choice for *E. coli* infections, being less effective and more costly than cycloserine. The majority of strains of *Klebsiella* are resistant. A follow-up study showed a 38% long-term failure rate, the possible causes of which are discussed.

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INDOMETHACIN: A NEW NON-STEROID ANTI-INFLAMMATORY AGENT

BY

F. DUDLEY HART, M.D., F.R.C.P. **P. L. BOARDMAN, M.B., M.R.C.P.**

The Rheumatism Unit, Westminster Hospital, London

The measurement of joint-swelling in the human subject is not easy, but in the assessment of drugs purporting to have an anti-inflammatory effect in conditions characterized by the presence of chronic inflammatory swelling, such as rheumatoid arthritis, some clinical measure is essential. We have found that the only practical and reliable measurement which can be done repeatedly and reasonably quickly in the wards is finger-swelling measured by jewellers' rings (Hart and Clark, 1951). All patients with active rheumatoid arthritis entering our wards have finger-swelling measured in this way twice weekly by the same clinician at approximately the same time of day as a routine measure. Also, the patient's own assessment of pain, stiffness, the number of analgesic tablets taken daily, the time taken to limber-up in the morning, and the clinician's assessment of grip strength, joint tenderness, and sedimentation rate are done routinely on all patients as measures of progress irrespective of the treatment given throughout their stay in hospital.

Measurable reduction of joint-swelling occurs regularly and demonstrably with steroid therapy, but not with salicylates, phenacetin, paracetamol, or the pyrazoles (phenylbutazone or oxyphenbutazone) as measured by this method ; and since the early use of the corticosteroids and corticotrophin no other therapeutic substances of the many we have tried have produced a measurable reduction in swelling of the interphalangeal joints. It was therefore a pleasant surprise when we found that in indomethacin (MK 615) we had the first non-corticosteroid agent which produced a predictable and measurable reduction in joint-swelling in most cases of active rheumatoid arthritis.

Chemistry

Indomethacin is a non-steroid anti-inflammatory and antipyretic agent. Its activity does not depend upon pituitary-adrenal stimulation and it is fully active in adrenalectomized animals. Chemically it is 1-(*p*-chloro-

benzoyl)-5-methoxy-2-methylindol-3-acetic acid, having the empirical formula of $C_{19}H_{16}NO_4Cl$ and a molecular weight of 357.8. It is relatively insoluble in water but soluble in the common organic solvents. It is rapidly cleared from the plasma, having a half-life of 0.3–4 hours in various species. From 46 to 63% of an intravenous dose of indomethacin-2-C^{14} is rapidly excreted in bile of dogs, guinea-pigs, and monkeys (Hucker, Zacchei, and Cox, 1963). Its anti-inflammatory activity can be demonstrated in rats by the cotton-pellet granuloma-inhibition test and by inhibiting oedema on subplantar injection of irritant agents. Granuloma inhibition can be observed by oral administration or by local application to the cotton pellet in the same animal. After oral administration to rats the drug appears to be well absorbed and gives an estimated plasma half-life of about 21 hours; about 90% of the drug in plasma is bound to the non-diffusable constituents. Excretion in rats is largely through the kidney, little being found in the faeces. The rat and the dog apparently tolerate the drug less well than does man or monkey.

Antipyretic activity has been demonstrated by inhibiting the fever produced by injection of *Escherichia coli* endotoxin in both rats and rabbits. Analgesic effects could not be demonstrated in mouse or rat by current methods. Toxic effects in rat, dog, and monkey consist largely of gastro-intestinal irritation, monkeys tolerating larger doses of the drug than rat or dog. Judged by the work on animals, gastro-intestinal toxicity seemed to be the only effect likely to occur in man, but early clinical trials in the United States of America indicated that it was usually well tolerated by the human digestive tract (R. Hodgkinson, personal communication, 1963).

Material and Method

Indomethacin has been used in the treatment of a group of patients in whom a clinical response might be anticipated from administration of a compound with anti-inflammatory, antipyretic, and possible analgesic properties (see Table I).

TABLE I.—*Overall Clinical Response in 99 Patients Treated with Indomethacin*

Disease	No. of Patients	Clinical Improvement	No Clinical Improvement	Inconclusive
Gout	15	13	1	1
Ankylosing spondylitis	14	11	0	3
Rheumatoid arthritis:				
Measurable soft-tissue swelling	15	8	3	4
No measurable soft-tissue swelling	37	14	14	9
Osteoarthritis	7	6	1	0
Miscellaneous	11	6	5	0
Total	99	58	24	17

At the beginning of the trial patients were started blind on either the drug or placebo. It was soon apparent that on the high initial dose of 300 mg. daily by mouth patients developed marked symptomatic improvement or side-effects, and, with few exceptions, were able to differentiate the true tablet from placebo. It was felt that a comparison against placebo would therefore provide less information than against other potentially anti-inflammatory agents such as phenylbutazone or the corticosteroids. In the absence of side-effects patients received a minimum of 14 days' therapy, and some have been on treatment for up to one year.

Indomethacin was used for the treatment of acute gout, ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis.

Gout

Fifteen patients (14 male, 1 female) with gout received indomethacin for the acute attack. It was given orally in high initial dosage and gradually reduced as symptoms and signs improved. The first four subjects received indomethacin 400–500 mg. in the first 24 hours, dosage then being reduced by 100 mg. every second day. This dose was found to require modification because side-effects occurred not infrequently and most acute attacks responded satisfactorily to a smaller amount of the drug. Subsequently 200–300 mg. was given in the first 24 hours in divided dosage, and this was gradually reduced to 100–150 mg. daily for five days, or longer if symptoms persisted. Patients were not given a maintenance dose between attacks. Plasma uric-acid estimations were performed during and after the acute attack, but these revealed no significant changes. Patients were asked to record their impression of the effect on the acute attack, the rate at which relief ensued, the extent of relief, the occurrence of side-effects, and the presence or absence of symptomatic rebound on cessation of therapy. An attempt was made to compare the response with that previously obtained from phenylbutazone, oxyphenbutazone, or colchicine.

Ankylosing Spondylitis

Fourteen patients with ankylosing spondylitis were treated with indomethacin. These patients had all suffered from the disease for at least two years and six had a history longer than 10 years. All had characteristic *x*-ray changes. All experienced considerable pain and had taken different analgesics for a long time. Ten of these patients received indomethacin 300 mg. daily in divided doses for 14 days and four received 200 mg. daily. When a steady baseline was obtained this was changed blind to placebo and rebound noted. Some patients received the placebo first. They were asked to assess their symptoms during this time and to compare the relief obtained from indomethacin with that previously obtained from phenylbutazone.

Osteoarthritis

Seven patients with osteoarthritis were treated with indomethacin; three of them had involvement of the hips, one severe disease in the knees, and three involvement of the cervical spine. They received indomethacin 150–300 mg. daily in divided doses for 14 days. They were asked to note any change in symptoms while on the drug and to compare this with the effect of phenylbutazone taken immediately before. Withdrawal symptoms on cessation of therapy were also noted.

Rheumatoid Arthritis

Patients with rheumatoid arthritis were treated with indomethacin and assessed not only on their symptomatic response but also by reduction of joint-swelling. This group of 52 patients was divided into those exhibiting measurable inflammatory features (15) and those with less active but painful disease (37). Initially, 300 mg. was given daily in divided dosage, but subsequently 50–150 mg. daily was found to produce similar change with a lower incidence of side-effects.

The patients with inflammatory features all suffered from classical rheumatoid arthritis, 7 out of 11 having positive sheep-cell-agglutination titres ranging from 1:32 to 1:512. The method of assessment varied according to whether the patient was seen regularly as an out-patient or was admitted to hospital. In-patients were assessed by

their own daily record of pain, stiffness, and morning limbering-up time. Twice weekly the size of the proximal interphalangeal joints was measured by standard jewellers' rings by one observer at the same time of day. Joint tenderness over proximal interphalangeal and metacarpophalangeal joints was recorded, as was the strength of grip, using a soft cuff inflated to a pressure of 30 mm. of mercury. A Westergren erythrocyte sedimentation rate (E.S.R.) was estimated each week. In addition, four in-patients with swollen knees were assessed by daily clinical examination. Out-patients were seen weekly and the severity of symptoms was recorded, as was their range of activity. Their disease was also assessed by joint size, tenderness, and grip strength. Anti-inflammatory effect was assessed by weekly change in swelling of the proximal interphalangeal joints.

No change in the basic rest-exercise therapy was made during the trial. The patient was started on an identical placebo and observed until a steady baseline assessment was obtained; the genuine tablet was then substituted and when the new baseline was established indomethacin was withdrawn and identical placebo restarted. In assessment of the patient's condition not only an improvement on introduction of the drug was required but also deterioration when the drug was withdrawn before the clinical response was considered positive. In addition to patients with rheumatoid arthritis and inflammatory disease, 37 without measurable soft-tissue swelling were treated with indomethacin and the same parameters assessed. These patients had classical rheumatoid arthritis and the sheep-cell-agglutination titre was positive (1:32 to 1:2,048) in 22. Eight were in-patients and 29 out-patients.

Miscellaneous

Eleven patients with miscellaneous disorders were treated with indomethacin to assess its influence on fever, as in glandular fever and Reiter's disease, and pain from non-inflammatory lesions such as bony metastases.

Results

Gout

Of 15 patients with gout, 11 noted a dramatic and rapid response with full symptomatic relief, two noted a moderate analgesic response without complete alteration of symptoms, one patient noted no effect, and one developed immediate side-effects. The following case histories demonstrate the rapid response that may occur.

Case 1.—A man aged 52, who was diagnosed as having gout in 1956 and had acute episodes several times each year, developed an acute attack in May, 1963. Indomethacin 100 mg. t.d.s. was started. After 100 mg. he noted a dramatic improvement, and within 24 hours pain and inflammatory features had settled completely. Colchicine had produced relief in previous attacks only after several days and diarrhoea had always followed. Phenylbutazone 500 mg. in 24 hours had produced some improvement, but with this drug full symptomatic control occurred only after four days or more. The patient felt indomethacin was quicker and more effective. Not all patients noted such benefit (see Case 6).

Case 2.—A man aged 62, who had suffered from gout since 1941, developed an acute attack involving the right carpus, the right elbow, and the left hand. After indomethacin 100 mg. he noted complete relief within four hours and was able to sleep the following night. The attack had previously been treated for four days with colchicine and phenylbutazone with little effect, and he had been kept awake at night by the pain.

Case 6.—A man aged 64 developed acute gout. Indomethacin 100 mg. t.d.s. resulted in mild symptomatic relief, but the joint remained painful and inflamed, and after 48 hours he developed acute gout in another joint. There were no side-effects. This may represent a failure of response, or it may be that indomethacin absorption from the gastro-intestinal tract was impaired. Response in previous attacks to phenylbutazone had been entirely satisfactory.

Case 8.—A man aged 34 was admitted for observation after a hand injury sustained in a road accident. The next day he developed acute gout in the right ankle. Colchicine 8 mg. in divided dosage in 48 hours had no therapeutic effect and diarrhoea ensued. Indomethacin 100 mg. was given and definite relief was noted within an hour. After a further 100 mg. he was able to walk a few steps and the signs of acute inflammation were reduced. He was maintained on 300 mg. daily for five days, in which time the acute attack completely subsided. After 48 hours he developed a feeling of muzziness and headache, but this cleared on chlorpheniramine ("piriton") 4 mg. q.d.s. and on reduction of the dose to 200 mg. daily.

Case 9.—A man aged 50, in whom gout was diagnosed in 1956, noted no relief and no side-effects on indomethacin 100 mg. t.d.s., but obtained relief within 24 hours from 4 mg. of colchicine in divided dosage. He was the only patient who obtained no relief whatsoever from indomethacin. There seemed some doubt on his history that he took sufficient dosage to obtain therapeutic effect, for he was against taking any new drug when his old favourite, colchicine, was available.

In Table II a comparison is made between phenylbutazone and indomethacin in the seven patients who had received both drugs for the acute attack. It was suspected that Case 7 did not take the indomethacin.

TABLE II.—*Comparison of Effect of Indomethacin and Phenylbutazone in Treatment of the Acute Attack of Gout*

Case No.	Indomethacin		Phenylbutazone		Preference
	Speed of Action	Degree of Relief	Speed of Action	Degree of Relief	
1	24 hours	Full	4 days	Full	Indomethacin
2	4 ,,	,,	—	Nil	,,
3	2 ,,	,,	—	,,	,,
4	24 ,,	,,	12 hours	Full	Phenylbutazone
5	2 ,,	,,	24 ,,	,,	Indomethacin
6	24 ,,	Partial	24 ,,	,,	Phenylbutazone
7	—	Nil	24 ,,	,,	,,

The speed of action is the time between the initial dose and the onset of symptomatic relief. The degree of relief was assessed when the maximal clinical improvement had occurred. Patient 7 is suspected of not taking indomethacin.

Ankylosing Spondylitis

Of the 14 patients with ankylosing spondylitis who were treated with indomethacin, nine noted marked relief from pain and thought indomethacin 100 mg. was more effective than phenylbutazone 100 mg., one had moderate relief of symptoms and considered 100 mg. of indomethacin equal in effect to 100 mg. of phenylbutazone, and one noted mild improvement, less than that obtained from phenylbutazone. Except for three patients with early side-effects necessitating withdrawal of treatment, all noted deterioration on blind introduction of placebo. Three patients had side-effects which prevented assessment. The following are examples of case histories of patients who benefited from indomethacin.

A Scotsman aged 48, with ankylosing spondylitis since 1945, was experiencing severe pain in the lower back and between the shoulders. Previous therapy included phenylbutazone 300 mg. daily, which resulted in mild symptomatic relief but was associated with the development of dyspepsia. On his own initiative he started taking compound tablets of codeine in large quantities, and, although this was hard to assess, he probably took 25 tablets daily. After some weeks he was admitted as an emergency to hospital unrousable and cyanosed from excess medication. He started on indomethacin 100 mg. t.d.s., and this was increased to 100 mg. q.d.s. This dose controlled his pain to an extent that enabled him to stop taking any other treatment. On stopping indomethacin he deteriorated to his previous state.

A man aged 38, who was diagnosed in 1952 as having ankylosing spondylitis, had episodes of severe low-back pain lasting from 10 to 21 days, with full remission of symptoms between attacks. On starting phenylbutazone 100 mg. b.d. he had partial relief of symptoms after three days. Any increase in dosage produced a rash. Indomethacin 100 mg. b.d. controlled symptoms completely within 48 hours.

A woman aged 27, with ankylosing spondylitis and peripheral joint involvement, was maintained on 12 units of corticotrophin daily. Indomethacin 100 mg. t.d.s. produced a marked improvement in pain and corticotrophin was reduced by 5 units a day. Within two days she developed a severe headache ; indomethacin was withdrawn and symptomatic deterioration ensued. Corticotrophin was increased to the original dose level and symptoms improved only slightly ; a further temporary increase of 5 units a day was required before her clinical condition was adequately controlled. Subsequently she was found to have a good clinical response to indomethacin 50 mg. once or twice a day, dizziness on 50 mg. t.d.s., and headache on 100 mg. t.d.s.

Osteoarthritis

Six of seven patients with osteoarthritis noted symptomatic relief. Four out of five in whom a direct comparison was made preferred indomethacin to phenylbutazone. One patient noted no change in symptoms.

Rheumatoid Arthritis

Eleven patients with rheumatoid arthritis with measurable inflammatory features were assessed. Eight were out-patients and three were in-patients. In addition, four in-patients with swelling of the knees were included, making a total of 15 patients with active inflammatory disease (Table III). Of these 15 patients, eight showed clinical improvement with reduction in joint-swelling and two were inconclusive in that no rebound occurred on cessation of therapy. The following are examples of patients who improved clinically and noted reduction of joint-swelling.

A woman aged 58, with rheumatoid arthritis of two years' duration (Fig. 1), was severely incapacitated by pain, and the knees in particular had deteriorated to such an extent that she spent much time in bed and did not go out of doors. She was maintained on prednisone 20 mg. a day and aspirin 60 gr. (4 g.) a day. Indomethacin 300 mg. a day produced a marked clinical improvement and reduction in ring size. When she was changed blind to placebo she deteriorated to such an extent that the house-physician, who did not know of the alteration, ultimately used pethidine for analgesia. On reintroduction of indomethacin she improved once more, and after five weeks was discharged greatly improved and able to take short walks. She has been on indomethacin for a year with sustained improvement and with no side-effects. She had previously had a partial gastrectomy for duodenal ulceration and was able to tolerate indomethacin satisfactorily. Butazolidin had been ineffective in dosage of 300 mg. a day.

A 38-year-old woman developed rheumatoid arthritis at the age of 36. Neither paracetamol nor aspirin produced significant symptomatic improvement. Indomethacin 100 mg. b.d. gave her a feeling of drunkenness after 24 hours, but this disappeared on 50 mg. t.d.s. Placebo was introduced blind and assessment showed deterioration ; improvement occurred on reintroduction of indomethacin.

TABLE III.—*Effect of Indomethacin Compared With that of Phenylbutazone in Ankylosing Spondylitis and Rheumatoid Arthritis*

Disease	No. of Patients	Better than Phenylbutazone	Equivalent to Phenylbutazone	Less Effective than Phenylbutazone	Inconclusive
Ankylosing spondylitis	14	9	1	1	3
Rheumatoid arthritis:					
With measurable soft-tissue swelling	15	8	—	3	4
With no measurable soft-tissue swelling	37	9	4	15	9

Five patients failed to show reduction in ring sizes on indomethacin. In two the explanation was probably that treatment was given for too short a time to cause much change, as it had to be stopped after a few days because of side-effects. Two patients probably did not respond because there was inadequate initial acute oedema to show measurable change. The fifth patient responded to corticosteroids but not to indomethacin.

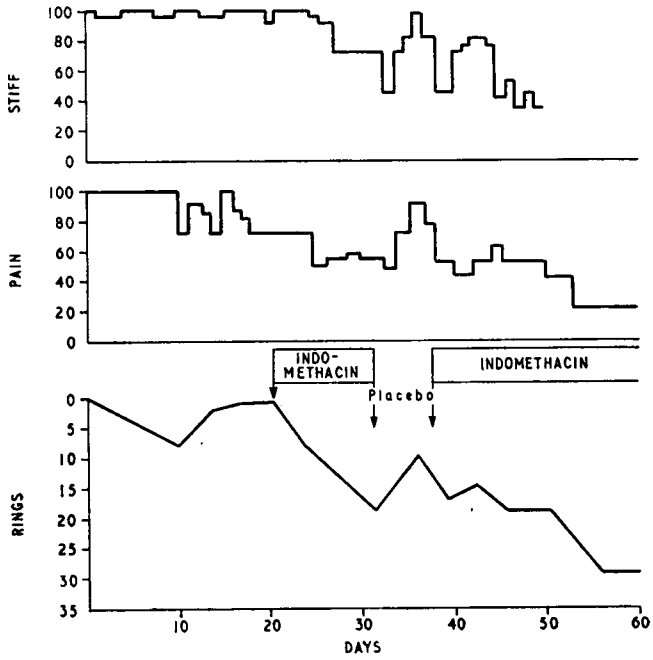

FIG. 1.—Chart of woman aged 58 treated with indomethacin for rheumatoid arthritis of two years' duration.

A man aged 61 developed acute rheumatoid arthritis over a period of nine months and required admission to hospital. As can be seen in Fig. 2, his condition was not improved by salicylates. Indomethacin was introduced without any pronounced effect and he was changed to corticotrophin. This resulted in clinical improvement and marked loss of inflammatory swelling.

In this case the rheumatoid disease was very active and a dosage of 60 units of corticotrophin was required initially to control the condition. In five cases where both drugs were used corticotrophin proved a much more effective anti-inflammatory agent than the new one.

Of 37 patients with rheumatoid arthritis without measurable inflammatory features, 14 noted a beneficial effect, 14 noted no effect, and in 9 the result was inconclusive. Of the 14 patients who noted a good effect 9 preferred indomethacin (100 mg.) to phenylbutazone (100 mg.), four noted a moderate improvement, equivalent to that obtained from phenylbutazone, and one noted mild symptomatic relief only. Of the 14 patients who noted no improvement on indomethacin, six benefited from phenylbutazone, while seven noted no effect ; one had not received phenylbutazone. Indomethacin was inconclusive in a further nine patients, eight of whom experienced side-effects and one developed an influenza-like illness and stopped taking the tablets. Six of these patients found phenylbutazone to be of value, two noted no effect, and one had never taken phenylbutazone.

Side-effects

Side-effects were frequent with indomethacin on a dosage of 300 mg. daily, occurring in 26 of 50 patients. Reactions

at this dose level usually occurred 48 to 96 hours after starting treatment. Seven patients who experienced side-effects on 200–300 mg. a day were found to be symptom-free on a smaller dose more gradually introduced.

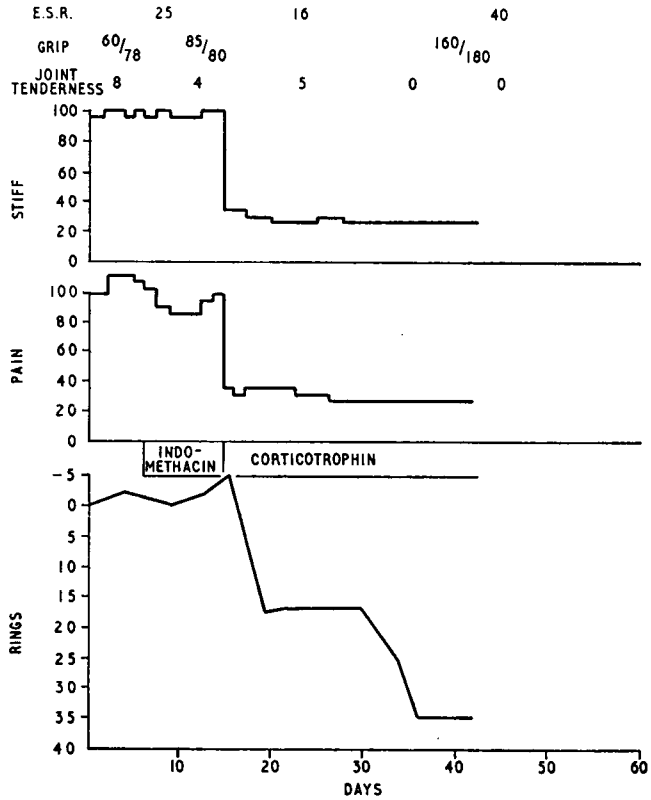

FIG. 2.—Chart of man aged 61 treated with indomethacin for acute rheumatoid arthritis with little effect.

Gout

Of 15 patients who received indomethacin for the acute attack of gout, three experienced side-effects. One developed a headache after 48 hours on 300 mg. daily, which cleared on 200 mg. a day and was relieved by an antihistaminic preparation. Another patient noted mild headache and giddiness on 400 mg. daily after 48 hours. Only one patient had a severe but transient reaction. This woman, aged 23, had hyperuricaemia, a family history of gout, and congenital hypoplastic kidneys, and was subject to acute gout. Her blood urea was 52 mg./100 ml. and uric acid 13.2 mg./100 ml. She took indomethacin 100 mg. for an acute attack of gout and within 10 minutes became drowsy, was unable to focus on any object, and later developed a severe throbbing headache. Symptoms improved after four hours, but the headache remained for 24 hours. Several cups of coffee reduced her drowsiness. The reaction was thought to be too rapid in onset to be accounted for by high blood levels of indomethacin due to impaired renal function. This was an abnormal incident, no similar reaction being observed in any other patient.

Rheumatoid Arthritis

Of the 52 patients with rheumatoid arthritis who received indomethacin, 31 noted side-effects. The age of these patients varied from 20 to 56. Symptoms developed within two to three days in 16. They occurred within six hours of the first dose in 10, and in five reactions were delayed until after six days. Patients usually experienced several side-effects at the same time. Of 37 patients with relatively inactive rheumatoid arthritis, 28 experienced side-effects, while only 3 of the 15 patients with measurable inflammatory disease were affected.

Headache occurred in 14 of 31 patients. This was characteristically a generalized throbbing in the head and ears: one was severe, eight were moderate, and five mild.

Giddiness was present in 12 patients. This was a sensation of unsteadiness without vertigo. It interfered with gait and driving a car. Three were mild, eight moderate, and one was severe.

Faintness, coupled with a sense of impending loss of consciousness, was experienced by two patients. This symptom occurred only when other side-effects were pronounced. In no case, however, was there loss of consciousness.

Muzziness and mental change : two patients noted muzziness with inability to concentrate or think out intellectual problems, two felt emotionally detached, and four said they felt drunk.

Nausea and vomiting : nine patients experienced anorexia and nausea, two of whom vomited.

Diarrhoea : four patients experienced diarrhoea. This was usually associated with nausea or vomiting.

Dyspepsia : four patients experienced dyspepsia, which was severe and necessitated cessation of treatment: one had no previous gastro-intestinal history, two were intolerant of phenylbutazone, and one, who had both a hiatus hernia and gall-stones, developed dyspepsia with soluble aspirin, paracetamol, and placebo tablets identical in appearance to indomethacin. Two patients developed dyspepsia within two days of starting the drug and the other two first noted symptoms after seven days' therapy.

Drowsiness : two patients developed drowsiness within one hour of the first dose. If they sat down they fell asleep. This symptom occurred only after the more severe reactions and was improved by taking coffee. Blurred vision was noted by these patients.

Side-effects usually cleared within 24 hours of cessation of treatment, but occasionally lasted for two to three days. Five patients were given antihistamines, chlorpheniramine 4 mg. q.d.s., and four noted improvement in the headache but not in gastro-intestinal symptoms.

The effect of a lower dose on side-effects has been studied in seven patients intolerant of high dosage. Of three patients who experienced side-effects on 300 mg. a day, two were symptom-free on 200 mg. and one on 150 mg. a day. Three patients with side-effects on 200 mg. daily were able to tolerate 150 mg. a day, and one of these who suffered side-effects on 100 mg. b.d. was found to become symptom-free on 50 mg. q.d.s. One patient, intolerant of 100 mg. a day, was maintained satisfactorily on 50 mg. a day.

Ankylosing Spondylitis and Osteoarthritis

Six of the fourteen patients with ankylosing spondylitis developed side-effects; four were taking 300 mg. a day, one of whom later had no symptoms on 200 mg. a day; one was on 200 mg. a day; and one on 100 mg. a day, experienced a mild headache.

Of seven osteoarthritic patients treated none noted side-effects.

Patterns of Side-Effects

Of 88 patients with disorders of the locomotor system treated with indomethacin, 40 (45.4%) suffered side-effects. These effects were commoner in patients with rheumatoid arthritis (59.6%) than with gout (20%). Side-effects included headache, giddiness, faintness, muzziness, mental

change, anorexia, nausea and vomiting, dyspepsia, diarrhoea, drowsiness, and blurred vision. More than one symptom occurred in all patients. Headache was improved by antihistamines, and drowsiness by coffee. Seven patients with rheumatoid arthritis and one with ankylosing spondylitis who had side-effects on relatively high initial dosage were found to be symptom-free on a lower dose more gradually introduced. It is probable, therefore, that with a starting dose of indomethacin 50 mg. daily and gradual increase by 50 mg. every third day to a maximum of 200 mg., the incidence of side-effects may be much lower than this figure. A dosage of 300–500 mg. daily may occasionally be used, but side-effects are likely to be frequent. There was no evidence of toxic effect on the blood, liver, or kidneys.

Side-effects occurred in four patterns: (1) Within a few hours the patient experienced severe symptoms independent of the dose. (2) Side-effects developed most often between 48 and 72 hours and were reduced by adjusting the dose. This appears to be a cumulative effect. (3) A small number of patients developed symptoms after seven days, as in two of the four cases of dyspepsia. (4) Some patients experienced muzzy feelings and mild headache about two hours after each dose, which wore off after an hour and did not progress. This occurred only with the 100-mg. tablet, never with 50 mg.

Discussion

It is clear that in indomethacin we have an agent that will reduce swelling and also relieve pain. As an anti-inflammatory agent it is less effective than the corticosteroids and corticotrophin, but it is the only non-steroid agent we have used to date which has produced measurable reduction in finger-swelling in active rheumatoid arthritis. In this disorder those cases with measurable inflammatory swelling did appreciably better and had fewer side-effects than those with less inflammatory change. In two cases the dose of corticosteroids previously needed to control symptoms was gradually reduced under cover of the new drug, but in 12 others it proved ineffective. The response in acute gout is, in our opinion, better than with any other therapeutic agents at present available, for its action is more rapid than is that of phenylbutazone and the patient is less subject to rebound attacks than with corticotrophin. The definite relief of pain in the few cases of osteoarthritis assessed makes it seem likely that the drug has analgesic properties independent of its anti-inflammatory ones, and its use in a few febrile cases demonstrated that it is also an effective antipyretic: in one case of glandular fever treated with indomethacin there was rapid improvement in symptoms and signs, with relapse as soon as it was discontinued.

As regards toxicity, it is clear that our initial dosage was too high and we now seldom use 100-mg. tablets, but favour 50 mg. one to four times daily. On this lower dosage side-effects are much less troublesome and the headache and muzziness which are the commonest complaints often pass off on continuation of low-dosage therapy. Many patients intolerant of other drugs because of gastro-intestinal side-effects are tolerant of indomethacin, which in our hands has proved relatively non-toxic in this respect to man, unlike the results in experimental animals. Time will show if there are any other side-effects, but at present no changes in blood counts or liver- or renal-function tests have been noted, nor were skin reactions seen. We have not used it in children or in pregnant women. On present evidence we consider that indomethacin, in spite of its tendency to cause headaches and dizzy feelings, has a definite part to play in the treatment of the chronic rheumatic disorders, and we regard it as the drug of choice in acute gout. In ankylosing spondylitis, osteoarthritis, and active rheumatoid arthritis it has also much to offer.

Summary and Conclusions

Indomethacin (1-*p*-chlorobenzoyl)-5-methoxy-2-methyl-indol-3-acetic acid) has proved to have anti-inflammatory and pain-relieving effects in gout and rheumatoid arthritis. It has also proved effective in the treatment of ankylosing spondylitis and osteoarthritis. At a dosage above 200 mg. a day headaches and dizziness were frequent, occurring in over 50% of those treated. At a daily dosage of 50–200 mg. side-effects occurred in 43%.

Dyspepsia has been rare—in 4 out of 99 patients. Also rare were faintness (2), drowsiness (2), and feelings of drunkenness (4). Intolerance or resistance to the drug has not been observed in up to one year of continuous treatment.

Indomethacin is the drug of choice in acute gout, where relief is obtained more rapidly than with phenylbutazone. It is useful also in ankylosing spondylitis, in osteoarthritis, and in cases of rheumatoid arthritis with inflammatory features and swelling of joints.

Although more time is needed before the true incidence of toxic effects can be evaluated, indomethacin appears to be a useful addition to the treatment of these rheumatic disorders.

ADDENDUM.—We have now followed up 123 patients for periods of up to one year; other workers have reported dyspepsia and occasional gastrointestinal haemorrhage as complications of indomethacin therapy. In our experience to date, only 4 out of 123 patients have experienced dyspepsia and none has had clinically detectable haemorrhage. Three of these four patients have suffered dyspepsia on phenylbutazone.

One patient who noted an initial symptomatic improvement on indomethacin has found that the symptoms have gradually returned in spite of continued treatment. This was thought to be due to the possible development of tolerance.

Three out of 123 patients developed skin lesions; one of these suffered from disseminated lupus erythematosus. The rash was irritating and consisted of discrete red macules and papules on the limbs. It disappeared completely within 48 hours of stopping the drug.

In one patient a reduction of the drug from 350 to 150 mg. a day resulted in the rash resolving.

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New Zealand is to replace its present Council of Scientific and Industrial Research with a national research advisory council on January 1, 1964. Its main functions will be to advise the Minister in charge of the administration of the Act that empowers this change on the promotion and development of scientific research and on its planning and co-ordination. (New Zealand House, August 30.)