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Phenylbutazone (butazolidin) and its therapeutic value today

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PHENYLBUTAZONE (BUTAZOLIDIN(R))
AND ITS THERAPEUTIC VALUE TODAY

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HISTORICAL

Phenylbutazone (Butazolidin(R)) is a comparatively new compound which appears to hold exceptional promise in the treatment of the various types of arthritis and allied musculoskeletal disorders. Also its experimental use in a greater variety of diseases has been of great interest and occasionally fruitful of somewhat astounding results.

Phenylbutazone was first synthesized by H. Stenzl in the laboratories of J. R. Geigy, Basle, Switzerland, in 1948. Prior to this time the compound had served as an excellent solubilizing agent for the relatively insoluble aminopyrine. Its first clinical application was in this combination with equal parts of aminopyrine in a preparation known as Irgapyrin(R) in Europe, and Butapyrin(R) in this country. (1) There were soon extensive clinical reports, principally from Switzerland and Germany (Belart, 1949; Wilhelmi,1950; Pulver, 1950; Kienle, 1950; Fischer, 1951), which indicated marked analgesic, anti-pyretic, and anti-inflammatory effects in various rheumatic diseases particularly following intravenous or intramuscular administration of Irgapyrin. When antirheumatic effects were claimed for Irgapyrin

it was suggested that perhaps the blood level of aminopyrine when it was injected must have been unusually high. But Currie (1952) found that the level was the same in rheumatic patients treated with Irgapyrin, (who alone claimed relief of pain) as in those treated with aminopyrine. He then investigated this new substance, supposedly inert, which the pharmaceutical firm of Geigy had synthesized merely as a solvent for the aminopyrine. (2)

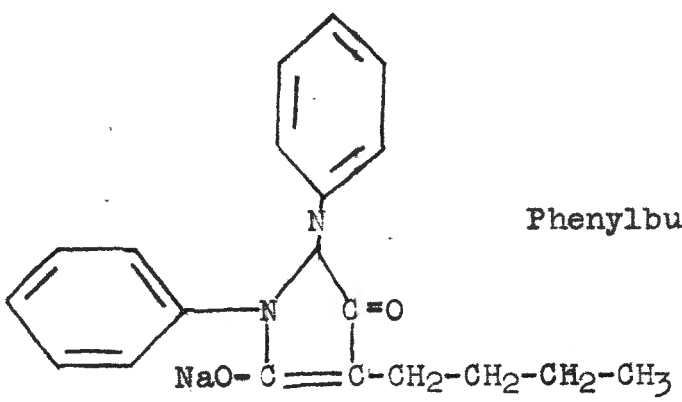
It was soon demonstrated that phenylbutazone by itself raised the pain threshold to electrical stimulation of nerve endings in rabbits, that it had an antipyretic effect in rabbits infected with Escherichia coli, and that it delayed the development of erythema on the skin of rabbits exposed to ultraviolet radiation (anti-inflammatory action). In the latter case phenylbutazone was found to be more effective than aminopyrine or the combination of the two. (3)

Because of occasional serious hazards of aminopyrine therapy and because some of the clinical results obtained with the combination of aminopyrine and phenylbutazone, or the latter alone, were superior to those obtained with aminopyrine alone, clinical investigations of phenylbutazone were undertaken with diligence. Here

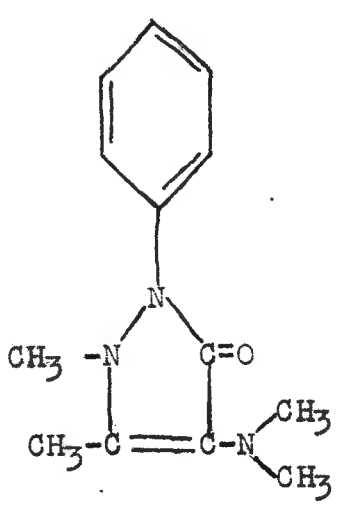
then we find the emergence of a new substance originally designed to be the vehicle of an antirheumatic analgesic only to come into its own and surpass the original agent in its own role.(4) The clinical trials of this new drug were begun in July 1951 and in England by June of 1952, 100,000 patients had received the agent.(5)

COMPOSITION

The pyrazole derivative designated phenylbutazone, has the chemical designation sodium-4-butyl-1, 2-diphenyl-3, 5-pyrazolidinedione. Its similarity to aminopyrine (4-dimethylamino-1, 5-dimethyl-2-phenyl-3pyrazolone) is noted from the structural formulae below. The substance is a slightly yellow or white crystallin powder and in the pure state has a somewhat bitter taste.



Phenylbutazone



Aminopyrine

PHARMACOLOGIC CHARACTERISTICS

Phenylbutazone has the character of an acid which is easily dissolved in water in the form of its sodium salt, a fact that facilitates the preparation of an injectable solution. Its rate of absorption, metabolic fate, and elimination is totally different from aminopyrine.(6) If both phenylbutazone and aminopyrine are administered simultaneously in the same dose to animals, the phenylbutazone persists in the blood stream in high concentrations for 12-24 hours (longer in humans), while aminopyrine disappears very quickly.(7)

Analgesic, Antipyretic, Anti-inflammatory, and Anti-Histaminic Effects

The clinical benefits of phenylbutazone seem to depend on three main properties: analgesic, antipyretic, and anti-inflammatory actions. Domenjoz(7) believes the analgesic and antipyretic properties are probably due to central mechanisms. He examined the analgesic effect by measuring the pain thresholds on electrical stimulation of the dental pulp in dogs and rabbits. He states that the intensity and character of the analgetic action of phenylbutazone are very similar to that of salicylates, pyrazoles, and phenacetine by his methods. To obtain comparable analgesic effects to morphine,

phenylbutazone must be administered in doses 10-50 times that of morphine. In clinical practice however, Currie(8) found phenylbutazone "compared poorly" with aspirin in the relief of pain associated with nonrheumatic disorders such as neuritis, neuralgia, and migraine.

Antipyretic action has been demonstrated in animals by artificially induced hyperthermia wherein boiled cultures of B. coli are injected into the animal.(7)

The anti-inflammatory effects were readily demonstrated by Domenjoz(7) After injecting egg albumen into the foot of a rat, he measured the amout of resultant swelling and edema by employing a plethysmometer. He found that by administering a prophylactic dose of phenylbutazone (200 mgm. per Kg.), the appearance of swelling retarded and the degree of inflammation was reduced. He attributes at least some of this anti-inflammatory effect to decreased capillary permeability. The phenylbutazone was more effective than aminopyrine when administered in identical amounts, and was also more efficient than either cortisone (40 mgm. per Kg.) or ACTH (8 mgm. per Kg.).

The experiments of Domenjoz showed further that after a prophylactic dose of phenylbutazone (100 mgm. per Kg.) guinea pigs could tolerate an amount of histamine

15-20 times greater than the lethal dose. But in tests with histamine-induced contraction of isolated gut, wheal tests and hypertension, there were no antihistaminic properties demonstrated. (7)

Absorption, Distribution, and Excretion

By using ultraviolet absorption techniques it was found that phenylbutazone is rapidly and almost completely absorbed from the gastro-intestinal tract. The peak plasma concentration of the drug is reached in approximately two hours following the administration of a single oral dose. Approximately one-third is concentrated in the plasma where it is strongly bound to plasma protein. The peak plasma level is not usually attained for 6-10 hours after intramuscular injection, the slower rate presumably due to local precipitation of the agent. (9)

On a repeated daily dosage of 800 mgm., the plasma concentration will usually reach a stable level on the third day. If more than 800 mgm. daily is given to an adult, there is an accompanying sharp increase in excretion of urinary metabolites. (1)

The inadequate therapeutic effects seen in some patients have been attributed to low plasma levels due to rapid biotransformation peculiar to some individuals.

The human metabolizes phenylbutazone at the rate of 15-25% per day (dogs and rats 90%) on an average therapeutic dosage of 600-800 mgm. daily, so that a period of seven to ten days usually elapses before the drug disappears from the blood stream.(9) It is not excreted as such in any significant amount. Studies are in progress to isolate and identify the three metabolites that have been detected in the urine in significant quantity. (10)

Effect on Electrolyte Balance

Fabre and Mach(11) were among the first to draw attention to the effects of phenylbutazone on electrolyte balance. They used the combination of phenylbutazone and aminopyrine and the effects described were attributed to the former. They observed a weight increase in 18 of 20 patients and in three there were clinical signs of edema. The increase in weight was maximum on the third to fifth day and not progressive thereafter. Within 24 hours after discontinuing therapy there was a diuresis accompanied by weight loss. This work is confirmed by Chenkin et al. (12)

Wilkinson and Brown (13) found there was a temporary decrease in urine volume with a significant retention of sodium and chloride ions. Potassium excretion is unaffected

and in this respect the action of phenylbutazone has the opposite effect of cortisone. Sodium retention begins at levels of about 50 mgm. per liter, while levels of 100 mgm. are required to obtain an anti-inflammatory effect in rheumatoid arthritis.(9) It has been found by means of creatin-clearance studies that the renal glomerular filtration rate is not affected by phenylbutazone, suggesting that tubular reabsorption is responsible for the decrease in excretion of water and salt.(13)

Effects on Clotting and Blood Vascular System

In studying 92 patients carefully, Weiner (14) attempted to determine the origin of the anemia in some patients treated with phenylbutazone. Many showed significant falls in hemoglobin concentration, with equivalent fall in red cell count and hematocrit values. That there was no accompanying change in reticulocytes, icteric index, or red cell saline fragility indicated no hemolysis and suggested no suppression of red cell formation. This he confirmed by P^{32} studies of red cell mass. His experiments prove quite conclusively that the seeming anemia present in phenylbutazone administration is in most instances, a simple hemodilution.

Weiner also studied the effect of the drug on the clotting mechanism in an endeavor to find an explanation for the occasional instances of gastro-intestinal hemorrhage. In 11 patients there was no observed effect on prothrombin time, antithrombin activity, recalcification time, prothrombin consumption, capillary fragility, or bleeding time. (14)

In contrast, 16% of 188 patients of Stephens et al.(4) had platelet counts below 100,000. The lowering of the count developed suddenly in some, slowly in others. Bone marrow examinations in two patients with counts below 30,000 disclosed no abnormalities and the megakaryocytes appeared to be normal. There was no evidence of petechiae or gross bleeding that could be attributed to the thrombocytopenia. Humble (15) found a "significant" increase of the clotting time and a prolongation of prothrombin time in six of 44 patients. There was a prompt return to normal after oral administration of vitamin K.

Agranulocytosis due to aminopyrine seems generally to be accepted as a sensitivity reaction and can be reproduced in the susceptible individual even with the most minute dosages. Kuzell and Schaffarzick (16) suggest that the agranulocytosis due to phenylbutazone

appears to be due to a direct depression and not dependent on individual susceptibility. Therapy was resumed without recurrence in three of their nine patients manifesting degrees of agranulocytosis. In the case reported by Hinz et al.(17) this viewpoint is also supported in that the granulocyte count began to rise even while the patient still had a concentration of phenylbutazone in the plasma in excess of 50 mgm. per liter and the drug was still present in easily detectable amounts at the time of recovery.

Effects on Tissue Metabolism

In the experimental animal receiving phenylbutazone there is an increase in the uptake of P^{32} by tissue ribonucleic acid as reported by Delfel and Griffin.(18) They suggest that the drug may increase the rate of ribonucleic acid synthesis or reduce its rate of degradation.

Phenylbutazone depresses the rate of I^{131} uptake by the thryoid both in the laboratory animal and in the human, presumably because of the ability of the drug to combine with iodide in the body. There have no clinical reports of disturbances of thryoid function.(19)(20)

It has also been shown that phenylbutazone causes some inhibition of oxygen consumption and glucose utilization in cerebral cortical tissue. This might explain the observation that large doses produce tonic-clonic convulsions in animals. No attempt was made to localize the precise region of the inhibition. (21)

Mode of Action in the Rheumatic Disorders

In the various forms of arthritis most consistent is the relief of pain, joint stiffness and swelling which allows significant increase in comfortable physical activity. After phenylbutazone therapy there are no X-ray findings in rheumatoid arthritis which cannot be accounted for other than on the basis of loss of joint swelling, edema, and congestion. Serial biopsy studies have shown no changes upon histological appearance of rheumatoid nodules. (22)

Both phenylbutazone and corticotropins are useful in rheumatic disorders, both induce retention of sodium and water, both reactivate peptic ulcers, and the mechanisms of both are yet somewhat obscure. This would suggest that phenylbutazone may be a simple stimulant of the pituitary-adrenal axis. However, laboratory efforts to validate such a theory have failed completely thus far. In adrenal cortex ascorbic acid depletion

tests on rats which had undergone hypophysectomy, corticotropin significantly diminished the adrenal ascorbic acid concentration while none of the pyrazolidines, (including phenylbutazone) did so , indicating that the latter compounds do not stimulate the adrenal cortex directly. (21) The same authors observed that in intact rats Irgapyrin and aminopyrine effected a reduction in adrenal ascorbic acid while phenylbutazone produced no such change. These observations suggest that aminopyrine may stimulate the anterior pituitary to release corticotropin, which in turn stimulates the adrenal cortex.

In another experiment, phenylbutazone did not maintain the adrenals of rats subjected to hypophysectomy. These observations reinforce the conclusion that the drug does not directly stimulate the adrenal cortex nor alter the pituitary-adrenal axis. Concurrent studies showed no changes in the circulating blood picture. (21)

It is of interest that in reports from India (23) where a group of patients with rheumatoid arthritis were treated with Irgapyrin(R) it was noted that the patients who improved showed a "statistically significant" reduction in the circulating eosinophils four hours after the injection of the drug. The authors would

suggest that the drug acts by stimulating the pituitary-adrenal system. Patients who did not improve after this therapy did not respond to stimulation of the pituitary-adreno-cortico system as there was no fall in circulating eosinophils.

Phenylbutazone does not appear to affect urinary ketosteroid excretion, eosinophil count, erythrocyte sedimentation rate nor the insulin requirement in diabetics. (24)(8) Thus it would seem that the mimicry between phenylbutazone and the hormones is not complete.

In their attempts to prolong the beneficial effect of cortisone, Gsell and von Reckenberg (25) studied the association of cortisone and phenylbutazone. The latter was given two to four weeks parenterally to make acute manifestations of chronic polyarthritis disappear. Their second stage of therapy then was to give 1.5 Gm. cortisone in 12-20 days. In the third stage phenylbutazone was given again. They state that phenylbutazone tends to maintain the beneficial results obtained with cortisone and prevent relapse. If the two are given concurrently the hazards of gastric ulcer, water retention, and granulocytopenia are greatly increased. However, others are of the opinion that in the concurrent use of the two, the toxicity of either

substance is not altered, and that smaller doses of each appeared to be effective. (26)

Initially phenylbutazone was considered to have a true antirheumatic effect. However, more recently many workers are somewhat doubtful of this. But Currie, who first introduced phenylbutazone in England, contends that it does poses this specific action in that it has a low analgesic potency in normal persons and animals, and in pain of nonrheumatic origin. Also in favor of such a specific action, in his view, was the prompt response to phenylbutazone in cases of rheumatic fever and gout. (15)

In attempts to determine the basis for the rapid benefits in gout, it is concluded that phenylbutazone is uricosuric, due to inhibition of renal tubular reabsorption of urate, while the glomerular filtration rate is unaffected. (50) The report of this work does not mention increased urinary urates after the phenylbutazone administration.

UNTOWARD EFFECTS

It is of interest to note that nearly one-half of the reports to date relate, the often varied, occasionally serious hazards in employment of this drug. By the latter part of 1952 and early 1953, reports of untoward reactions were of frequent occurence in the various journals, but in recent months their number has again dropped in favor of further descriptions of pharmacologic specificities and therapeutic achievements.

The reported work shows a wide range in rates of toxicity. Currie (15), whose experience now includes well over 1,000 patients, states that the incidence of toxic effects in his patients was "insignificant". Stevens (4) had some manifestation of untoward effect in 44% of his patients. European workers generally have reported lower rates of toxicity than have the Americans.

It is noteworthy that in an early series by Kuzell et al. (21), an incidence of 34% toxicity was reported. More recently Kuzell's incidence is reported at 40%. (26) In the interval between these reports he made a study of the pharmacologic characteristics of the drug (10) and yet his toxicity rate is higher in the later series. The average of all reports is 25-30%. There is somewhat more agreement, however, in the percentage of patients

in whom because of toxic effects, it was necessary to discontinue the agent. This was generally about 10%.

As in the experience of some of the antibiotic agents the early reports concerning the hazards of this drug related instances of agranulocytosis. Stifel and Burnheimer (27), Bershoff (28), and Steinbrocker (29) were among the first to report this reaction. Crowther (5) says that phenylbutazone is a dangerous drug and if doses of more than 1.2 gram per day are used, the door is open to agranulocytosis.

The patient of Stifel (27) after six weeks of 200 mgm. phenylbutazone three times daily for severe rheumatoid arthritis (with relief of symptoms), went five days with "complete absence" of granulocytes. He says that it is "certainly not a toxic reaction, but a hypersensitivity that takes some time to develop". Ceasing of administration of the drug, and employing ACTH (or cortisone) is followed by prompt return of the granulocytes.

Granirer (30) stated that hematemisis, anorexia, and nausea without previous history of stomach disorder, were in his experience the most commonly encountered symptoms.

In the recent exhaustive work by Kuzell et al. (26), water retention was the most frequent manifestation --14% of 800 cases. Hemming (10) reports the most

commonly reported reactions are gastro-intestinal upset, edema, and drug rash. Others report epigastric pain and nausea as the most frequent complication and this was readily controlled by administration of antispasmodics and aluminum hydrdxide preparations. (31) Kuzell (32) states that the nausea is at least partially due to a central effect, and that the use of coated tablets, gelatin capsules or antacids seems to make but little difference. Others report that in all but five of 30 patients with nausea and vomiting, medication was continued by taking alkalis or aluminum gels. (33) The early reports of gastro-intestinal hemorrhage (16)(4)(30), are based on reactivation of peptic ulcer.

Besides the above mentioned, other reported toxic symptoms are anemia (16)(4)(31), stomatitis (16)(30)(34), vertigo (16)(31), nervousness (16), euphoria (4)(35), hematuria (4)(35), fall in platelets (4)(26), salivary gland swelling (31), insomnia (4)(32), drug fever (36)(34), hypertension (26), hepatitis (26), and palpitation, dyspnea, and blurred vision (15)(30).

In an usual case cited by Charet (34), after three weeks of phenylbutazone therapy the patient complained of severe dysphagia, blephorspasm, and dysuria. Fishman (36) reports a case of near fatal exfoliative dermatitis. His patient, a 60 year old white female,

took 200 mgm. four times daily, and developed a rash on the fourth day. She saw a physician after one week by which time she had a generalized, confluent morbilliform rash with swelling of all extremities. She was treated with hydrocortisone , antihistamines, and potassium permanganate baths. He states that her reaction acted like a serum sickness for the nine months that followed. He concludes that a rash can continue to progress even after the drug is stopped and can develop into a nearly fatal exfoliative dermatitis. This would take issue to statements that the rash will subside rapidly after discontinuance, or that it may be safe to continue therapy after desensitization by smaller doses.

Five deaths attributed to phenylbutazone therapy have been reported. Nathan (37) reports the case of a 60 year old female who had been receiving 800 mgm. daily for 17 days. Death was rather sudden and "apparently related" to the effects of the drug, either toxicity or hypersensitivity in the skin and viscera. Prominent at the autopsy were adrenal cortical cell degeneration and a nonspecific myocarditis. There were also vascular degenerative and necrotic lesions throughaut the viscera. The case of Steinberg (38) is

quite similar.

In another case (39) there was sudden death in a 74 year old man after eight weeks of therapy, Death was apparently due to an overwhelming septicemia resulting from an agranulocytosis although he had been having weekly blood counts. Corticotropins were not employed here. One death in Europe was attributed to superficial gastric ulceration promoting hemorrhage, after five weeks of therapy.(40) In another, the fatality was due to bronchopneumonia in an elderly male who had developed agranulocytosis, and who had received no ACTH or cortisone. (40)

In one recent series of 800 cases (26) the incidence and severity of toxic manifestations was the least in the treatment of gout, in which also the therapeutic response was the greatest. In mixed rheumatoid and osteoarthritis the incidence and severity of untoward reactions were greater, and the phenylbutazone therapy was less rewarding in this group. The authors suspect a true inverse relationship between the therapeutic benefit and the number of side reactions in each disease group. They would show a relationship in order of decreasing importance in the following order: gout, psoriasis with arthritis, ankylosing spondylitis,

ankylosing spondylitis, rheumatoid arthritis, painful shoulder, malum coxae senilis, osteoarthritis, osteoporosis, and mixed arthritis.

It is suggested that the age of the patient does not appear to influence the occurence of toxicity significantly. Males experienced toxicity in 29%, females 43%. There was but little appreciable toxicity in doses not exceeding 600 mgm. daily. They were able to administer gold (aurothioglucose) concurrently with the phenylbutazone in 66 patients with no increase in incidence of toxic manifestations. (26)

THERAPEUTIC MANAGEMENT

Anyone who has used phenylbutazone clinically to any extent or who has read any of the recent literature must be both impressed by its therapeutic achievements and on the other hand its toxic manifestations. Perhaps many practicioners are witholding trials as the vividness of the latter presses upon their minds. It would be most ideal then to know who should receive this drug, for how long, how much, what can be expected, and what should be done to forestall any serious untoward effects.

There is agreement on one point at least, and that is that all workers believe that when phenylbutazone is indicated, it should be given only under adequate medical supervision. Patients for phenylbutazone therapy should be selected with care. A history of peptic ulcer should be regarded as a complete contraindication, at least to oral administration. (10) The activation of preexisting peptic ulcers is to be considered as the most serious side effect. The concurrent use of antacids, as previously mentioned, is advantageous and often employed, as are enteric coated pills. Parenteral administration has been recommended in questionable cases, but one instance of activation

of ulcer during intramuscular administration has been reported. (21) Some are of the belief that epigastric pain is unrelieved by antacids and antispasmodics. (26) But to minimize gastric irritation the drug should always be taken immediately before or after a meal or with a full glass of milk.

In most instances of weight gain, water retention, or edema, the treatment is satisfactory by complete withdrawl of the drug, if only for a short time, or reduction of dosage and/or dietary sodium restriction. Because of this control, water retention has not been a serious complication unless the patient had a borderline cardiac decompensation. These patients have responded to digitalis, but in order to prevent any cardiac embarassment phenylbutazone should be withdrawn, Constipation is often an early sign in patients experiencing fluid retention. (32) A weeks time is often necessary following discontinuance of therapy before frank edema disappears. Some are of the opinion that mercurial diuretics are ineffective in this sutuation (26)(31), but others (33)(13) have employed them with satisfactory results. The use of phenylbutazone in the presence of cardiac, renal, or severe hepatic disease should preferably be in a hospital.

In most instances the cutaneous manifestations are

nonpruritic macular lesions which fade readily, The rash is generally more florid in the areas exposed to the sunlight. The majority of rashes fade promptly on cessation of the drug and many are able to resume the previous dosage without any further consequences. Cortisone, in dosage of 75-100 mgm. daily for two to three days frequently hastens the disappearance of the rash. If a purpuric rash is suspected vitamin K should be employed. (15)

Although the likelihood of granulocytopenia is remote, the desirability of conducting periodic blood counts in all patients receiving the drug is self-evident. Additionally, the patient should be warned to report immediately the occurence of soreness of the mouth, throat, anus, vagina, or fever.

As a safety measure Steinbroker insists on a weekly leukocyte count, and he believes that a break in the treatment of a few days every two weeks is a worthwhile procedure as a safeguard against toxic reactions. (15) Others suggest that the patient be given only enough of the drug to last between the weekly checkups. (28) The weight of the patient is closely checked and inquiries made as to the nature and color of bodily excretions.

Currie (15) suggests that his low incidence of toxic reactions compared to other observers might be attributed to the fact that he always stops the administration of all other drugs when the patient receives phenylbutazone. It is known that the toxicity rate is increased by the simultaneous administration of barbiturates and aminopyrine. (15)

In most instances the average effective dose of 600-800 mgm. daily in divided amounts, will provide satisfactory results. In the absence of symptoms of intolerance, the dose may be increased cautiously if therapeutic effect is not obtained. But once the improvement has been obtained on this higher dosage, a gradual downward adjustment should be made until the minimal level required for maintenance is reached. Some patients are reported to be well maintained on dosages as low as 100 mgm. daily. (41)

Kuzell states that rheumatoid arthritis usually requires 600-1200 mgm. daily for maintenance. (32) On the other hand, Stephens states that there is little to be gained by increasing the dosage above 600 mgm. daily for the same disorder. (4)

Acute gout is usually treated with 800-1000 mgm. daily with maintenance at 200 mgm. daily. In the treatment of relatively transient conditions such as tendinitis, bursitis, and capsulitis the phenylbutazone may discontinued a few days after symptoms have been

completely relieved. But in the event of relapse, subsequent attacks are usually as responsive to treatment as the first, and therapy may be conducted on similar lines. The action of the drug is usually manifest by the third to fourth day and it is seldom necessary to continue trial therapy beyond a week in the absence of a favorable result. (41)

The most convenient mode of administration is of course by mouth. In favor of parenteral administration are the advantages of enabling the physician to maintain close supervision over the patient, occasionally preventing gastric distress, and at times a somewhat more rapid result in acute cases. When given parenterally the injection should be deep into the buttock and injected slowly.

In order to reduce the likelihood of granulocytopenia, it is considered unwise to use X-ray therapy or to employ any drug known to depress hemopoietic function at the same time phenylbutazone is being used. Females who have had toxic goiters are said to be prone to nervous manifestations with the use of phenylbutazone, and in such a case 100 mgm. every second day would be a proper trial dosage. (32)

THERAPEUTIC RESPONSE

The musculoskeletal disorders in which phenylbutazone has been most commonly employed are discussed in the order of decreasing response to the therapy of the drug as is most generally agreed upon by the majority of observers.

Gout

There is general agreement that phenylbutazone is more effective here than in any of the other disorders discussed. In treating 60 patients with all types of arthritis Kidd (42) reports "the most remarkable" effect was the quick arrest of acute gouty arthritis.

In the early series of Kuzell et al. (16), 74 patients were treated. Approximately one-half had complete clinical remission in 48 hours after institution of therapy. "All patients had some degree of clinical response." The serum uric acid promptly decreased although there was no consistent increase in the urinary excretion of uric acid.

Mason (15) states that the urinary excretion of uric acid in a given patient depends on the balance between water retaining and mild uricosuric actions.

It was noted that among 408 patients with painful musculoskeletal disorders other than gout, there was appreciably less beneficial effect of phenylbutazone in those patients who had elevated serum uric acid than in those with normal uric acid levels. (43)

In the latest series of Kuzell et al. (43), 83% of 200 patients voiced major improvement, and in only 3% was there a failure to respond. The drug was administered in coated tablets of 100 or 200 mgm. or in gelatin capsules. To a number of patients it was given intramuscularly in a 20% solution of its sodium salt at doses of one gram. The usual procedure in the more acute cases was to give one gram intramuscularly followed by 400-800 mgm. daily by mouth. In the early months of this study the oral daily dose ranged from 100 -1600 mgm., but later rarely exceeded 600 mgm. The most rapid relief usually followed the parenteral administration, and occasionally in less than an hour there was relief of pain, swelling, and erythema of the part. The response to the drug was slightly better in the males. It was more effective in both sexes than colchicine, salicylates, or hormones in the acute stages, maintenance therapy, and prevention of exacerbations. Occasionally corticotropin brings about the more rapid relief. (43)

Other observers had results showing a somewhat lower response. Byron 74% (31), Gutman 82% (44), Rowe et al. 53% (45), and Kidd 61% (42).

Ankylosing Spondylitis

Following the use of phenylbutazone here, the decrease in stiffness and pain has been more marked than in rheumatoid arthritis, but generally much of the effect of the medication is dependent upon continuous administration.

Stephens et al. (4) in a series of 32 cases observed "increased motion in the back" in 44%, " four plus subjective improvement" in 80%, and minimal objective improvement in 18%. Those who did benefit had an accompanying increase in chest expansion and weight.

In the early series of Kuzell et al. (16), there was major improvement in 80% of 21 cases. In the later series of 51 patients there was the major improvement in 65%. (26) When comparison with X-ray therapy was possible, more than one-half had more relief with the phenylbutazone. Where comparison could be made with cortisone or hydrocortisone, five were better with the phenylbutazone and five were more comfortable on the hormones.

Steinbroker (33) reports 68% major improvement, Kidd et al. (42) 61%, and Byron (31) 66%.

Rheumatoid Arthritis

The greatest volume of reported observations on clinical trials of phenylbutazone are those in which patients with rheumatoid arthritis were treated. The difficulties of measuring the various features of rheumatoid arthritis are great. In interpreting the results of the observers, clearly no more than approximation can be attempted in comparing the effects of two different agents, when administered and observed by two or more individuals. The results have been less encouraging than in acute gout or ankylosing spondylitis. Generally the workers who had the best results used higher dosages and in turn had greater percentages of untoward reactions. Table I lists the results of a number of observers.

Newns (15) reported relief of symptoms in 70% of both advanced and early cases of rheumatoid arthritis. Of 197 of his patients, 65% were still taking the drug after six months; 13% gave up the treatment because of absence of any effect from the beginning; 7% because the initial benefits wore off, and 14% because of toxicity.

TABLE I
(after Hemming (10))

Author	No. of Patients	Therapeutic Response
Rowe et al. (45)	16	Good response in 69%; subjective improvement 95%; objective 29%
Smith and Kunz (41)	16	"As long as the drug was given at least 75% improvement in all patients in pain, mobility."
Patterson et al. (35)	32	"marked to moderate relief of pain, swelling, and stiffness in 72%"
Byron and Orenstein (31)	40	Complete to considerable response in 92%.
Kidd et al. (42)	51	32% subjective improvement; objective improvement "infrequent"
Davies et al. (46)	70	"improvement impressive and at times dramatic"
Currie (8)	81	95% subjective improvement; 29% objective improvement.
Steinbrocker et al. (33)	117	"significant analgesia" in 50%
Kuzell et al. (26)	163	Complete to considerable improvement in 59%.

In the early series of Kuzell et al. (21), considerable improvement or complete remission was observed in 72%. In the later series (26), 59% had similar results and here the dosage was "rarely" above 600 mgm. per day while in the earlier report the dosages ranged to 1600 mgm. daily. But according to Steinbroker (33),

there was no noticeable association between improvement and total dosage, once maximum effectiveness had been established. Currie reports "highly significant" results in 30% of 81 cases treated by one gram intramuscular injections for ten days.(8) He also reports that 82% of 131 patients maintained on treatment for a year or longer are still improving and that none had failed to enjoy continued relief of symptoms.(15)

There generally appeared to be some correlation between objective improvement and the degree of functional capacity, with the greatest response seen in patients with the least initial disability. In the patients with rheumatoid arthritis of short duration there seemed to be more benefit than in those with prolonged involvement.(33) This is substantiated by the results in a group of patients treated with Irgapyrin in which the amelioration of symptoms was directly proportional to the duration of the disease. (23)

Contrasting somewhat with this is that in a given patient the joints which had been affected longest responded the earliest. The smaller joints of hands and feet responded better than the larger joints. (47)

There were no consistent changes in specific laboratory data. Eosinophil counts showed no significant variations. The sedimentation rate in about

one-third of the cases was found to have increased. It was decreased in one-third and unchanged in another third. Those patients in which a fall in sedimentation rate was demonstrated, the dosage could be reduced early and even discontinued for a relatively long period of time. (31)

Mason (48) observed a slight fall in sedimentation rates (7 mm,) and suggests that it is no more than that which may be produced by bed rest. Patterson et al. (35) reported that in none of theirs was a complete clinical remission brought about, a sedimentation rate lowered, nor than a minimal amount of swelling reduced. The sedimentation rate generally tends to rise during early stages of treatment, sometimes nearly doubling before decreasing. It is suggested that the response is not related to the sedimentation rate. (41)

Fifteen patients, each of whom had one or more previous treatments of gold therapy, were given 800 mgm. daily. Without exception, after the first dose the patients noticed improvement, and almost without exception within a day the pain had subsided. Here again the maximum improvement in the joint swellings was achieved within three days. (47)

In one series (16) while in no case was phenylbutazone superior to cortisone or corticotropin, the

incidence of side effects was greater with the hormones. Cortisone acetate and phenylbutazone were used alternately in several patients, each for a period of two weeks with satisfactory results. The patients in these instances felt generally stronger while taking cortisone. To observe the comparative effects of phenylbutazone and ACTH, six cases were studied in detail. (48) It was concluded that there was no evidence that the former has a"cortisone-like effect". Phenylbutazone appeared to be "roughly comparable" to ACTH in its effect on the features of rheumatoid arthritis in which pain is an important element.

Osteoarthritis

Here again the reports are less impressive. In general the results showed the greatest benefit in those cases designated coxae malum senilis, or more so than in the more unspecific cases of osteoarthritis. Most optimistic of the reports were those of British workers who in treating osteoarthritis of the hips used one gram intramuscularly every other day for five doses, followed by one gram every third day. The degree of relief experienced by these cases was "most impressive". (46)

In 51% of 116 patients Kuzell et al. (26) report major symptomatic improvement. Others report major

improvement in 43% (33), 30% (45), and 48% (31).

Mixed Arthritis

The response in the socalled mixed cases of arthritis in which the patient is said to suffer both rheumatoid and osteoarthritis, was less than in either of the specific reported types. Some believe that in certain cases hypertrophic arthritis may be a contraindication to the use of the drug when it exists in conjunction with rheumatoid arthritis. (41)

In general, a major improvement of 29% is reported with about one-third of the cases noting no benefit. Butapyrin is said to be of equal benefit as phenylbutazone in these cases. (26)

Miscellaneous

There are many conditions in which the value of phenylbutazone cannot be regarded as established. Following are conditions in which the drug has been favorably employed: psoriatic arthritis (21)(33), lumbosacral sprain (33), malignancy (31), lymphoma (51), osteoporosis of spine (21), scleroderma with arthropathy (33), acute peritendonitis (21)(33), acute myofibrositis (16), Hodgkin's disease(51), herniated disc (16)(33), capsulitis (41), postmenopausal arthralgia (33),

epicondylitis (41), reflex dystrophy (33), rheumatic fever (32)(49), bursitis (42)(41), fibrositis (31), and calcific tendbnitis (33).

The so called painful shoulder would comprise patients with peritendonitis, capsulitis, or acute bursitis of the shoulder region. The response here was very good with relief of pain and progessive increase of motion after 48 hours. (41)(26)

In epicondylitis, a condition which is often very resistant to X-ray therapy, manipulation, and local injection, "rather remarkable" results have been obtained. (41)

The subsidance of symptoms in acute rheumatic fever is at least equivalent to that following the use of salicylates. (32) In five cases of acute rheumatic fever which showed little or no response to salicylates and/or penicillin, the use of phenylbutazone is reported. (49) The patients aged 9-17 years, received 400-600 mgm. daily. In each case there was a rapid improvement (2-5 days) in joint pain, temperature, sedimentation rate, and the patients made a good recovery. There were no toxic reactions and the relapse which occured in one case on withdrawl of phenylbutazone, was quickly checked by a few additional doses.

In two patients with metastatic carcinoma in which hourly administration of narcotics were required, phenylbutazone was given with the result that narcotics were necessitated only 2-3 times daily, although there was no effect on the outcome. In a patient with a fibrosarcoma of the pharynx and metastatic involvement of the lung with pulmonary oteoarthropathy phenylbutazone was given. After five months under cortisone therapy with very little influence on the arthropathy and development of edema in both lower limbs, the administration of phenylbutazone was followed by a startling reaction, Joint symptoms cleared up and the edema of the lower extremities disappeared within a few days. (31)

In a recent report on 35 patients with Hodgkin's disease, phenylbutazone was administered in doses of 400-600 mgm. daily over periods ranging from two weeks to a year. The drug was reported effective in control of pain and fever, and occasionally in the improvement of appetite, and lessening of fatigue. A few patients had temporary relief of pruritis and regression of lymph nodes. (51)

The reports of phenylbutazone therapy in these varied complaints are encouraging and further observations will be of much interest to the medical profession.

SUMMARY

A review of the literature is made of the reports on the drug phenylbutazone, a pyrazole derivative now being marketed by the Geigy Pharmaceutical Company under the name Butazolidin.

The agent was first synthesized in 1948 and was used originally as an adjunct in promoting the solubility of aminopyrine for the treatment of the various types of musculoskeletal disorders. The compound with equal parts of each was sold in Europe under the name of Irgapyrin, and in this country by Butapyrin. It was soon found that the administration of phenylbutazone alone resulted in generally greater benefits and fewer toxic reactions than the original agent or compound.

Phenylbutazone is a pyrazole derivative similar to aminopyrine but with an additional benzene ring and a hydrocarbon side chain. It is termed by some to be a specific antirheumatic agent but the majority of observers believe the clinical benefits probably depend mostly on its analgesic, antipyretic and anti-inflammatory properties. It is thought that the analgesic and antipyretic actions are central mechanisms, and that the qualitative effects of these two properties are similar to salicylates, pyrazoles, and phenacetine. It has been

shown that phenylbutazone decreases the oxygen consumption and glucose utilization in cerebral cortical cells and that overdoses promote convulsions in animals. The somatic anti-inflammatory action is more potent than any of the aforementioned agents and also cortisone as demonstrated by experiments using a plethysmometer. The relief of joint swelling and stiffness resulting from this potent action allows significant increase in physical activity. In favor of the agent being a specific antirheumatic is its relative failure to relieve the pain of neuritis, headache, and neuralgia. The antihistaminic properties are as yet not fully defined, but it has been shown that laboratory animals will tolerate doses of histamine much in excess of the lethal dose following a prophylactic dose of phenylbutazone.

Phenylbutazone is almost completely absorbed from the gut and little is to be gained by intramuscular administration. One-third of the drug is combined with plasma proteins and its ultimate fate is as yet not fully determined. Levels of 100 mgm. per liter plasma are required to obtain a significant clinical benefit, and at levels of one-half this amount sodium retention begins by means of increased tubular resorption, and salt and water retention is the result. There may follow a

hemodilution with a laboratory picture of anemia, or edema if with continued administration, increased dosage, or renal disease. There has been no demonstration of adverse offects on the mechanisms of blood coagulation. Thrombocytopenia has been reported but no bleeding could be attributed to it. This and granulocytopenia are believed due to a sensitivity reaction in susceptible individuals and not as a toxic action as such. The drug acts to increase the rate of ribonucleic acid synthesis or reduce its rate of breakdown. Another effect in which the significance is as yet unknown is that it decreases the rate of I^{131} uptake by the thyroid.

Both phenylbutazone and corticotropins are of benefit in arthritis, and both induce water retention and activate peptic ulcers. In laboratory work on rats that had undergone hypophysectomy, phenylbutazone did not decrease adrenal ascorbic acid, nor did it support the adrenals in these animals. There has been no proof that phenylbutazone directly stimulates the adrenal cortex, nor alters the pituitary adrenal axis. Urinary ketosteroids, circulating eosinophils, red cell sedimentation rates, and insulin requirements in diabetics are unchanged. Serum uric acid is decreased although there is no increase in the urinary excretion.

The use of phenylbutazone and cortisone alternately has been satisfactory in some hands, but when given concurrently untoward reactions have been reported as increased. Gold therapy has been given concurrently with no increase in toxic manifestations.

Wide ranges of toxicity rates from "insignificant" to 44% are reported. It has been necessary to discontue the drug in approximately 10% of all patients because of side effects. The most serious side effects have been those with hemorrhage and perforation of peptic ulcers, and granulosytopenia. Other reported reactions are rash, edema, anorexia, nausea, vertigo, stamatitis, euphoria, nervousness, thrombocytopenia, hepatitis, drug fever, salivary gland swelling, blurred vision, palpitation, and dyspnea. Three deaths have been reported as attributed to agranulocytosis and one to gastric hemorrhage. In another fatality, diffuse vascular degeneration with necrotic lesions throughout the viscera were found at autopsy. Females have a slightly higher rate of side reactions than males.

Weekly blood counts, weight check and physical examination are advised for those undergoing therapy. Intervals without treatment for several days is reported as helpful in lowering the incidence of untoward reactions. A history of peptic ulcer or cardiac decompensation are

contraincications, and preferably in renal or hepatic disease. Age as such is not a contraindication. Water retention is generally controlled by dietary sodium restriction and epigastric distress by antacids and the administration of the drug on a full stomach. Rashes and other minor effects can usually be controlled by decreasing the dosage, or cessation of administration if only temporarily. Thrombocytopenia and agranulocytosis are controlled by administration of vitamin K and ACTH respectively, and discontinuing the drug.

The usual therapeutic dose is 600-800 mgm. daily in divided doses. Maintenance therapy is individualized to the minimum, with many patients obtaining maximum benefits on 100 mgm. per day.

There appears to be an inverse relationship between therapeutic benefit and side reactions. The disorders in order of decreasing response to phenylbutazone and increasing rates of untoward reaction are: acute gout, psoriasis with arthritis, ankylosing spondylitis, rheumatoid arthritis, painful shoulder (including bursitis, tendonitis, and capsulitis), malum coxae senilis, osteoarthritis, osteoporosis, and mixed arthritis.

CONCLUSIONS

-1- The mode of action of phenylbutazone has not been fully determined.

-2- There is no strict agreement on whether or not phenylbutazone has a specific antirheumatic action. The benefits obtained by its usage probably are due to its analgesic, antipyretic, and comparatively potent anti-inflammatory actions.

-3- There has been no proof that phenylbutazone directly stimulates the adrenal cortex nor alters the pituitary-adrenal axis.

-4- Phenylbutazone therapy does not appear to influence significantly urinary ketosteroids, circulating eosinophils, erythrocyte sedimentation rate, nor blood sugar levels in man.

-5- Untoward effects have been reported in up to 44% of patients receiving the drug. The average rate of side effects approaches 25-30%.

-6- Patients to receive phenylbutazone must be selected with care. Peptic ulcer and cardiac decompensation or the history of either, and known sensitivity to the drug are contraindications. Frequent regular blood and physical examinations

must be given all patients receiving the agent. Each patient must be individualized as to amount of dosage and length of treatment.

-7- Of the musculoskeletal disorders in which phenylbutazone therapy has been used to any extent, patients with acute gout receive the greatest beneficial effects. The rate of complete remission to major improvement approaches 75%. Approximate rates of major improvement in reported cases of others are: ankylosing spondylitis 64%, rheumatoid arthritis 60%, osteoarthritis 30%, and mixed arthritis 26%. The descriptions of the various other disorders are encouraging, but the role of phenylbutazone has not been fully determined in all.

-8- In cases of arthritis other than gout, phenylbutazone appears to have the greatest beneficial effect in those patients with a low level of serum uric acid.

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