

OBSERVATIONS ON THE TREATMENT OF RHEUMATOID ARTHRITIS WITH BUTAZOLIDIN

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Introduction

From its introduction into Europe in 1640, cinchona bark (and then quinine) was the only reliable antipyretic drug known until, in 1875, the antipyretic action of salicylic acid was discovered. This was followed by a period of intense activity in the examination of the quinine molecule and the synthesis of new febrifuge drugs which would be free from the undesirable side-effects produced by quinine and salicylic acid when administered frequently and in large doses. Although the fashion of strict antipyresis passed, these researches had started the production of a group of the most valuable and frequently employed remedies in the field of practical therapeutics. For convenience, these drugs are grouped together pharmacologically as the "new antipyretics", although they are no longer commonly employed for the purpose which their name implies. It has long been recognized that, apart from their action on fever, all these drugs possessed, in varying degree, the ability to relieve the discomfort and pains associated with many febrile states, and it is as "alleviating remedies" that they are now mainly used.

One of these synthetic drugs was antipyrin (1884) which was formed in an endeavour to produce a synthetic quinine-like substance. As Alstead (1940) commented:

That the result was such a valuable remedy as antipyrin was, in reality, a lucky chance, for both the conception of the composition of quinine, which served as a type, and the conception of the composition of the antipyrin first obtained were erroneous.

Although the attempt to synthesize quinine had failed, a new ring—pyrazol—had been formed, and this led to the synthesis of yet another compound—amidopyrine.

Amidopyrine, being relatively insoluble, was more

slowly absorbed than antipyrin and was found to have a more prolonged, though less powerful, antipyretic action.

As experience with these "new antipyretics" grew, evidence accumulated that they were mild, yet effective, analgesics, and, further, that this analgesic property was most marked in the so-called "rheumatic" and "neuralgic" types of pain. So far as the pain of rheumatic disease was concerned, the salicylates and the pyrazol derivatives were most notably effective. This has been commented upon by many writers (*e.g.* Sollmann, 1917; Cushny, 1910; Poulsson, 1938) since they were first employed. Indeed, the combined antipyretic and analgesic properties were so obvious in the treatment of acute rheumatism that the drugs were regarded as being virtually specific in their action on this disease.

Evidence began to accumulate that amidopyrine was a possible cause of agranulocytosis, and its use, in both Great Britain and America, has become progressively less popular. The salicylates, however, continue to be the sheet-anchor in the drug treatment of acute and sub-acute rheumatic disease, and are believed not only to alleviate the symptoms, but to shorten the course of the disease. The mode of action of the salicylates, however, remains obscure. Recently, attempts have been made to explain this action on the basis of adrenal cortical function (*e.g.* Blanchard and others, 1950; Pfeiffer and others, 1950). Amidopyrine is still extensively employed on the Continent where many physicians regard it as an effective analgesic in rheumatic conditions in which salicylates have failed.

For some years we have been investigating the disproportionately effective analgesic action of these new antipyretics in "rheumatic" diseases, and certain observations appear to us to be satisfactorily established.

(1) Salicylates and amidopyrine are capable of reducing

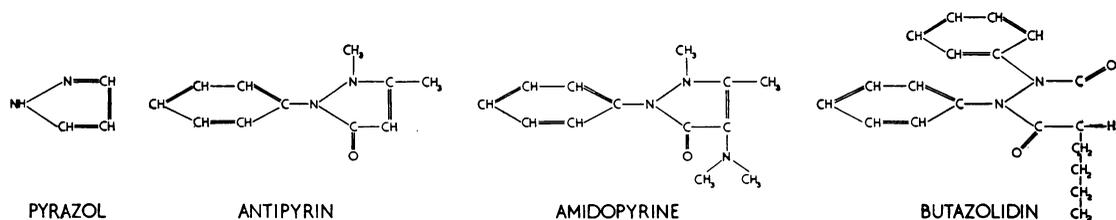


Fig. 1.—Chemical composition of pyrazol, antipyrin, amidopyrine, and Butazolidin

fever and of diminishing joint pain, tenderness, and swelling in acute rheumatic infection.

(2) In rheumatoid arthritis, salicylates are less effective in the control of pain than amidopyrine, but the effect of both drugs is more pronounced than that of the newer and more generally effective anodynes such as pethidine, Physeptone, and Heptalgin.

(3) In some cases of rheumatoid arthritis the administration of antipyrin and amidopyrine is followed not merely by symptomatic relief, but by some reduction in joint swelling and peri-articular oedema and inflammation.

It appeared, therefore, that it might be useful to investigate the effect of pyrazol derivatives on rheumatic disease and not merely as strict antipyretics. The introduction of cortisone provided a yardstick of anti-rheumatic activity and also led most rheumatologists to agree fundamentally on criteria of improvement.

While amidopyrine was being investigated the therapeutic activity of Butazolidin—yet another pyrazol body—was discovered (see Formulae, Fig. 1). Butazolidin was then applied to the treatment of non-articular rheumatism and rheumatoid arthritis (Currie, 1951, 1952).

Since the production of Butazolidin (some 7 months ago) in sufficient quantity to allow of wide application and trial, a number of papers have been published dealing with the drug both clinically and experimentally. We have now applied Butazolidin to the treatment of 424 cases of rheumatoid arthritis, and while so doing, have endeavoured to establish a safe and effective scheme of dosage. This paper is intended to present our findings and to review them in the light of other published work.

Pharmacology

The action of the drug has been studied in two ways:

- (1) Work on experimental animals.
- (2) Clinical application.

(1) Experimental Work.—Butazolidin is chemically 1·2 diphenyl 3·5 dioxo 4-n butyl pyrazolidine, and the graphic formula is as previously shown. It differs

both in constitution and physico-chemical properties from those pyrazol compounds previously employed in medicine; thus it has the characters of an acid and its sodium salt is easily soluble in water. Pulver (1950a, b) has shown that, unlike amidopyrine, it persists in the blood in high concentrations for 12-24 hrs after administration. The absorption, metabolism, and excretion of the drug have been very fully investigated in animals by Pulver (1950a, b), Pulver and Wilhelmi (1952), Rechenberg and Pulver (1951), Wilhelmi (1949, 1950, 1951, 1952), and Wilhelmi and Domenjoz (1951). It has been shown to possess three main properties (Wilhelmi and Domenjoz, 1951):

- (i) analgesic;
- (ii) anti-inflammatory;
- (iii) antipyretic.

Analgesic.—The effect of the drug on the threshold for electrical stimulation of the dental pulp was tested by Domenjoz and Wilhelmi. The techniques used were those of Koll and Reffert (1938) for dogs, and Gordonoff and Ruckstuhl (1939) for rabbits. These experiments showed that Butazolidin had an analgesic action similar to or less than that of small doses of salicylate, phenacetin, and amidopyrine, but that it did not approach the analgesic effects of morphine.

Anti-Inflammatory.—The anti-inflammatory effects of Butazolidin on the oedema caused by the injection of (i) egg albumin, and (ii) formalin, into the legs of rats was studied by Domenjoz (1952), Theobald (*cited by* Domenjoz, 1952), and Wilhelmi (1949-52). They showed that the oedema-inhibiting effects of injecting subcutaneously 200 mg./kg. Butazolidin were greater than that of cortisone 2×10 mg./kg., 2×20 mg./kg., and 2×50 mg./kg., or of ACTH 4×2 mg./kg. This action of Butazolidin was also demonstrated (Wilhelmi, *cited by* Domenjoz, 1952) in experimental inflammation produced by other methods, thus:

- Ultra violet light dermatitis in rats.
- Mustard oil chemosis in rabbits.
- Arthritis in immunized rabbits after intra-articular injection of antigen.

Domenjoz (1952) has demonstrated diminished capillary permeability to colloidal dyes after Butazolidin administration, and marked anti-histaminic effects in the perfused rabbit ear and in the guinea-pig. It seems

possible that these effects contribute to the anti-inflammatory effects of the drug.

Antipyretic.—The antipyretic action of the drug has been demonstrated by Wilhelmi and Domenjoz (1951) in yeast fever in rats and in *B. coli* pyrexia in rabbits.

(2) Clinical Application.—The most marked therapeutic effect of the drug in cases of rheumatoid arthritis is relief of pain. With the doses we employ, almost all patients experience relief within 2 or 3 days of beginning treatment. Synchronously there is lessening of stiffness in affected joints and performance improves. We have already emphasized that these effects may all be part of the analgesic action. After 7 to 10 days' treatment a reduction in joint swelling can be demonstrated in a proportion of cases; this appears to be most noticeable in early and acute cases. It is possible that the differing percentages of patients showing reduction in joint swelling reported by *e.g.* Kuzell (1952), Kuzell and others (1952), Stephens and others (1952), Steinbrocker and others (1952a, b), and ourselves (Currie, 1951; Brown and Currie, 1952), depends upon the number of early or acute cases in the groups treated. The erythrocyte sedimentation rate and plasma viscosity are reduced in some patients, particularly in early and acute cases. This feature is much more marked, however, in the treatment of acute rheumatic fever, in which disease also the antipyretic effect is striking (Fleming and Will, 1953).

Apart, however, from these particular effects, it appears, as Kuzell and his colleagues also comment, that the drug has some general anti-rheumatic effect. In the case of rheumatoid arthritis the effect of the drug appears to be to suppress the activity of the disease, while in rheumatic fever the whole course of the disease appears to be greatly shortened. It has been alleged (*B.M.J.*, 1952a), that all the effects reported or confirmed in cases of rheumatoid arthritis could be explained on the basis of the analgesic action of the drug. This appears to be unlikely, for drugs known to be much more powerful analgesics than Butazolidin (*e.g.* Physeptone, Heptalgin, pethidine) fail to produce anything like similar relief.

In addition to its effects on rheumatic conditions, however, Butazolidin has been shown to have a number of other therapeutic applications. Thus Kuzell (1952) is of opinion that its most striking application is in acute gout and chronic gouty arthritis. Engleman and others (1952) claim that the blood uric acid is markedly diminished after Butazolidin administration, although there is "no striking uricosuria". Steinbrocker states that many conditions respond to Butazolidin administration, and mentions two cases of peri-arteritis nodosa, which

had previously responded only to ACTH, and were controlled by Butazolidin. Similarly, Kling (1952) alleged that his best results were obtained in eight cases of spondylitis ankylopoietica which had failed to respond to x-ray therapy and cortisone; six showed great improvement in a few days, and the erythrocyte sedimentation rate fell from 45 to 25 mm./hr.

Studies of the blood Butazolidin content after intravenous, intramuscular, and oral administration led us to the following conclusions:

- (i) The drug is rapidly and almost completely absorbed from the alimentary tract.
- (ii) Absorption after intramuscular injection is irregular; we believe that there may be some precipitation of the drug at the site of injection in some cases.
- (iii) Oral administration is the method of choice, not only because of its ease and simplicity, but also because of the regular and adequate absorption which follows its employment.

Considerable variation appears to occur in the rate at which Butazolidin is removed from the blood (in the patients studied, from 15 to 45 per cent. per day; 75 per cent. showed a value of between 20 per cent. and 25 per cent. per day).

We have found that for suppression of symptoms in rheumatoid arthritis a blood concentration of 8-11 mg. per cent. appears to be required. This is effected in a majority of cases by an initial dose of 800 mg. in the first 24 hrs, and can be maintained with subsequent doses of 200 mg. daily (Figs 2 and 3, opposite).

Davies and others (1952) pointed out that no advantage appears to be gained by raising the daily dose above 1.0 g., and with this we agree. But, further continued high dosage does not, in our experience, result in continued increase of the concentration of Butazolidin in the blood, and we have found that the blood level becomes fixed at 12.5-15.5 mg. per cent. (Fig. 4, opposite). The drug does not exhibit cumulative features in patients, and this is in accord with Pulver's findings in experimental animals. Our investigations have also indicated that, although an initial blood level of 8-11 mg. per cent. is required to suppress symptoms, remission can be maintained by considerably lower concentrations of 4.6 to 8.0 mg. per cent. We have found, too, that initiation and maintenance of clinical improvement, and relapses, follow closely the pattern of the level of the drug in the blood. It would thus appear that the varying requirements of different patients in respect of maintenance doses is related to the rate at which they metabolize the drug. Because of this variation in the rate of Butazolidin metabolism in different patients we have evolved the following dosage

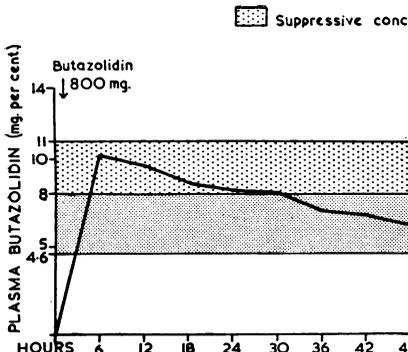


Fig. 2.—Plasma butazolidin concentration after a single dose of 800 mg.

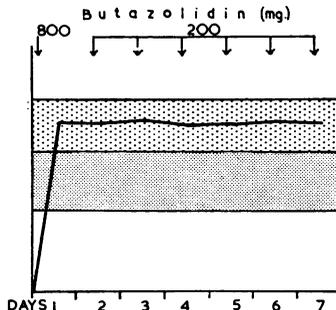


Fig. 3.—Plasma butazolidin concentration in a patient treated according to our dosage schedule

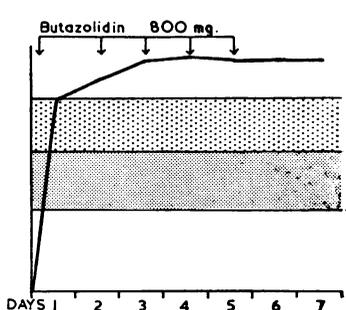


Fig. 4.—Effect on plasma butazolidin of repeated large doses (800 mg. daily)

schedule which meets the requirements of almost all cases (Table I).

TABLE I
DOSAGE SCHEDULE

Day	No. of Doses	Amount (mg.)
First	4	200
Second	3	200
Third	3	200
Fourth	2	200
Fifth	2	200
Sixth	1	200

If, by the fourth day of treatment, there is no subjective improvement, we estimate the blood Butazolidin level. If this is found to be within the "suppressive" level, we discontinue the drug as evoking no response. If, however, the blood level is inadequate for suppression of symptoms, we either increase the dose or give the drug by intramuscular injection. The latter alternative is indispensable where the keratin-coated pills are passed by the patient in the stools. Should symptomatic relapse occur on a maintenance dose of 200 mg. daily, the dose is increased to 200 mg. twice daily. If higher doses are required for maintenance, the blood level of the drug is estimated. If the patient remains improved on 200 mg. daily, the frequency of the dose is diminished to every other day.

Results

The results of treatment by Butazolidin in 424 cases of rheumatoid arthritis are set out in Table II.

TABLE II
ANALYSIS OF RESULTS

No. of Patients	Subjective Improvement	Improved Performance	Objective Improvement
81 (previously reported)	77	77	24
343	327	319	105
424	404 (95 per cent.)	396 (93 per cent.)	129 (30 per cent.)

The diagnostic criteria used were these:

- (1) Acceptable clinical history.
- (2) Polyarthritis.
- (3) Radiological confirmation or lack of evidence of other joint disease.
- (4) Normal blood uric acid.
- (5) Negative Wassermann and Kahn reactions.
- (6) Negative Widal test for abortus fever.
- (7) Negative gonococcal complement-fixation test.
- (8) Raised erythrocyte sedimentation rate and/or raised plasma viscosity.

The criteria of improvement are set out in Table III.

TABLE III
CRITERIA OF IMPROVEMENT

Subjective or Symptomatic	Objective
Pain and tenderness	Joint measurements
Performance	Reduced erythrocyte sedimentation rate and plasma viscosity
Well being	Appearance of joints

The erythrocyte sedimentation rate was ascertained repeatedly in 42 patients; in four it fell within the first 10 days of treatment, and in a further eight cases within one month of beginning treatment.

The results again illustrate the subjective nature of performance tests.

In the patients treated in this series, symptomatic improvement, when once established, was invariably maintained so long as the drug was continued.

Many of these patients have been on the small maintenance doses we have described for 6 months, seven for 11 months, and two for 12 and 13 months respectively. Improvement in performance has been seen to continue steadily in some patients even on very small doses.

Toxicity.—In the series of cases here reported, the incidence of toxic side-effects has been notably low (4.7 per cent.), and those that occurred were mild in nature (Table IV). Of the 424 patients treated, twenty showed side-effects during treatment, and in only three did treatment have to be stopped.

Other reports of Butazolidin therapy have given a varying incidence of toxic effects from 0-100 per cent. (Table V).

The heading "Miscellaneous", in Table V, includes thrombocytopenia, anaemia, leucopenia, purpura, epistaxis, haematuria, euphoria, insomnia, dyspnoea, vertigo, palpitation, "substernal pressure", stomatitis, "blisters of mouth", "intertriginous lesions", auricular fibrillation, fever, jaundice, "swelling of face", and injection abscess.

Besides these toxic effects, three deaths have been attributed to the drug, one from haematemesis and

TABLE IV
INCIDENCE OF TOXIC SIDE-EFFECTS

Nature of Reaction	No. of Cases	Comment
Oedema	4	Disappeared in two cases despite continued treatment, and in the other two only when the drug was withdrawn
Albuminuria	3	All cleared despite continued treatment
Skin rash	4	Possible alternative causes in three (phenobarbitone, enema, and shellfish respectively); drug readministered to these without reappearance of rash. Fourth patient also sensitive to morphine, codein, and iodoform
Nausea	6	Drug continued in all
Stomatitis	1	No granulopenia. Drug re-administered without recurrence of stomatitis
Tachycardia	1	Transient, drug continued
Tingling of toes	1	Transient, drug continued

TABLE V
TOXIC SIDE EFFECTS REPORTED BY OTHER AUTHORS

Author	Date	No. of Cases	Toxic Reactions						
			Total	Nausea Vomiting Dyspepsia	Oedema	Haematemesis or Melaena	Agranulocytosis	Skin Rash	Miscellaneous
Bach	1952	50	4	2	—	—	—	—	2
Bourne	1953	not stated	5	—	1	—	—	—	4
Crowther and Elgood	1952	"small series"	"frequent"	—	—	—	1	—	—
Davies and others.. .. .	1952	100	16	25 only 2 severe	8	—	—	3	3
Gillhespy	1952	15	1	—	—	—	—	1	—
Granirer	1952	20	20	—	6	2	—	4	8
Hart and Johnson	1952 a and b	16-60	14	2	3	—	—	6	—
Hogarth	1952	not stated	not stated	—	—	—	—	—	—
Jarvis	1952	not stated	1	—	—	—	1	—	—
Kelly	1952	not stated	"few"	—	—	—	—	—	—
Kersley and others	1952	14	—	—	—	—	—	—	—
*Kuzell and others	1952	140	47	24 some very mild	17	—	—	6	5
Loxton and others	1952	50	11	—	3	—	1	5	2
Shulman	1952	237	3	—	2	—	—	"a few mild"	1
Slot	1952	4	0	—	—	—	—	—	—
†Steinbrocker and others	1952b	52	13	4	3	—	—	3	9
Stephens and others	1952	188	83	9	9	2	—	9	54
Tait	1952	not stated	not stated	—	—	—	1	—	—

* Error in addition from paper quoted.
† Some patients showed two toxic features; tabulated under both.

two from agranulocytosis (*B.M.J.*, 1952b; *Lancet*, 1953).

In considering these reported toxic effects, three points must be borne in mind:

- (1) Not all symptoms occurring during drug therapy are necessarily due to the drug.
- (2) The evidence incriminating Butazolidin in many reports may be described as being, at best, presumptive.
- (3) The toxicity of any drug must be weighed against the benefits conferred by it. At the worst, Butazolidin compares very favourably with orthodox chrysotherapy in this respect.

We attribute the low incidence of toxic side-effects in our own group of patients firstly to careful dosage, and secondly to careful selection of patients, avoiding the aged and all suspected of having a poor cardiac reserve. With regard to two reported toxic features (dyspepsia and agranulocytosis), we would offer the following observations. Nausea, anorexia, abdominal discomfort, and vomiting have not been seen since we began to use enteric-coated tablets. The fact that Butazolidin is, like amidopyrine, a pyrazol derivative may have led to the anticipation of similar blood changes to those ascribed to amidopyrine. We have already drawn attention to the very different rates of absorption, metabolism, and excretion of the two substances as well as their physico-chemical dissimilarity, and it would therefore appear probable that their toxicity may also be different. Indeed, von Rechenberg has administered Butazolidin, in gradually increasing doses, to three patients who had recovered from amidopyrine agranulocytosis. The patients were known to respond with a rapidly developing granulocytopenia to minute doses of amidopyrine, but all tolerated full doses of Butazolidin without alteration in the number or type of the circulating leucocytes.

Conclusions

- (1) Butazolidin administration affords rapid and substantial relief to a large proportion of patients suffering from rheumatoid arthritis.
- (2) In many cases there is, in addition, an apparent suppression of the activity of the disease.
- (3) Almost all cases relapse slowly on withdrawal of the drug.
- (4) With careful dosage and selection and management of patients, the drug appears to be remarkably free from serious toxic properties.

Summary

The preliminary work leading to the therapeutic trial of Butazolidin is described.

The literature dealing with the drug experimentally and clinically is reviewed.

The results of treatment in 424 cases of rheumatoid arthritis are presented.

A plea is made for careful selection of cases and moderation in doses.

We wish to thank Dr. J. C. Eaton for carrying out the estimations of plasma Butazolidin content (by his own modification of Pulver's method), and Dr. J. W. Macfarlane for again, so willingly, placing beds at our disposal.

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**Remarques sur le traitement de l'arthrite
rhumatismale par la butazolidine****RÉSUMÉ**

On décrit le travail préliminaire de l'essai thérapeutique de la butazolidine.

On passe en revue la littérature sur l'aspect clinique et expérimental de ce médicament.

On présente les résultats du traitement dans 424 cas d'arthrite rhumatismale.

On préconise un triage soigneux des malades et une posologie modérée.

**Observaciones sobre el tratamiento de la
artritis reumatoide con butazolidina****SUMARIO**

Se describe el trabajo preliminar del ensayo terapéutico de la butazolidina.

Se pasa en revista la literatura sobre el aspecto experimental y clínico de este producto.

Se presenta los resultados del tratamiento en 424 casos de artritis reumatoide.

Se aboga la selección cuidadosa de los casos y la moderación posológica.