is obstructed by swelling of the mucosa it may be of benefit to blow oxygen on the obstructed part. It is safe to say that we became more and more conservative in regard to bronchoscopy as time went on, the general impression being that the amount of secretions increases after bronchoscopy. Tapotement and "squeezing" of the thorax seemed to have much greater effect, especially if suction from the bronchi was done simultaneously. Frequent changes in position are also of importance, to avoid atelectasis.

Problems of Organization

Previous to this epidemic no anaesthetist had ever worked regularly at the fever hospital. Now we were suddenly faced with the problem of recruiting a minimum of 40 persons trained in anaesthesiology who could cover the following field of work: (1) anaesthesia for the tracheotomies; (2) ventilation of tracheostomized patients; (3) cleaning of the lungs, treatment of atelectasis; and (4) treatment of shock. It took us only a few days to find that this work could not possibly be covered by the already functioning personnel without help from outside on a large scale. At one time during the epidemic, when 900 poliomyelitis patients had already been admitted, 75 patients were under manual artificial ventilation on the same day. For this it was necessary to employ 250 medical students to do the ventilation, 260 nurses from outside to sit at the bedside and attend to the patients' requirements, and 27 hospital workers to change cylinders and control the machinery: within these 24 hours 250 10-gallon (45.5-litre) cylinders were used.

The working plan of the anaesthetists was this. Each of the four big hospitals (the University Hospital, the Municipal Hospital, the Bispebjerg Hospital, and the County Hospital) covered a 24-hour period with its anaesthesia staff, under the direction of the senior anaesthetist, who spent the full period in the fever hospital. He did the anaesthesia and supervised his assistants. The latter, together with the epidemiologists and the otologists, supervised the medical students. Usually there was one anaesthetist in each of the three wards where the patients with respiratory and pharyngeal paralysis were treated. The anaesthesia staffs of the other Copenhagen hospitals (Finsen Institute, Orthopaedic Hospital, Municipal Chest Hospital) formed a very useful reserve.

At a relatively early stage it was decided to have lung physiotherapists working with selected patients who were apt to develop repeated atelectases. This arrangement proved very successful, and a total of 34 physiotherapists were active during the period of the epidemic. As previously mentioned, the procedure seemed most beneficial when physiotherapist and anaesthetist worked together.

It would take too long to go into details regarding the organization of the other groups of personnel. The organization and distribution of the patients were briefly mentioned in the introduction.

Technical Problems

When news about the epidemic had spread in Copenhagen equipment of all kinds poured into the hospital in a steady stream. It was soon found necessary to co-ordinate all these different types of material and also make an attempt to standardize the equipment. For this reason one man (an engineer) was appointed as consultant to the hospital. All requisitions went through him, and he, on the other hand, promised to procure the items with no delay. This system turned out to be a very good one.

The different types of respirator were supplied by various firms. A large number were borrowed from the other Scandinavian countries.

Equipment Around a Patient Under Manual Artificial Ventilation.—Oxygen cylinder with nitrogen and oxygen in 50% mixture. Reducing valve and flowmeter. Compressed-air cylinder with regulator, and injector suction aggregate. To-and-fro system (see Diagram) with two canisters and bag.

A special problem is the soda-lime for the canisters. Most preparations contain too much dust and present a potential danger of blowing dust into the patient's lungs. Actually only two preparations were suitable for use in this kind of treatment. Another problem was that the stores of soda-lime in Denmark were much too small to cover the demand, and we had to send for help from Great Britain, Sweden, and Norway several times: we got the help very promptly. It is estimated that about 100,000 blood-pressure measurements were taken during the five months, and there had to be a large number of B.P. cuffs in the hospital.

Anaesthetic Equipment.—Two anaesthetic machines, transportable, with suction; laryngoscopes with two blades; tracheal tubes in all sizes, with and without cuff; introducer for tubes; masks in three sizes; extra reservoir bags; airways of all sizes; suction catheters of different types with glass connexions; and stomach tubes. All equipment was kept in the operating-room, and was packed on trays and in boxes for immediate use in any part of the hospital where tracheostomies might have to be done. Furthermore, in each of the three wards an emergency set with equipment for manual intermittent positive-pressure ventilation and for intubation was kept. Finally, the admission ward was equipped with the previously mentioned complete set for the team which would go out to the provincial hospitals.

Conclusion

This report is an attempt to answer some of the questions of practical interest to those who will be concerned with the treatment of a large group of patients with poliomyelitis and respiratory and/or pharyngeal paralysis under emergency conditions. We have omitted the theoretical deliberations, which will all be found in the report under preparation and also in the paper which follows.

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EFFECT OF PHENYLBUTAZONE ON URIC ACID METABOLISM

BY

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Phenylbutazone ("butazolidin") has been said to be effective both in acute gout and in the later chronic stages. Amongst the varied clinical effects of this drug such claims stand out as of particular interest. Kuzell and his colleagues (1952) found that it had "a marked analgesic effect" on the acute attack within a few minutes, and other workers have confirmed this (Kidd *et al.*, 1952). There is, however, considerable disagreement about its effect, if any, on uric acid metabolism itself. Most workers are agreed that lowered blood uric acid levels follow the administration of phenylbutazone. Kuzell *et al.* claimed a "striking diminution of serum uric acid in all patients treated," without, however, putting forward any data. There followed the interesting suggestion that this lowering of blood levels was not associated with a comparable increase in uric acid excretion in the urine (Kuzell and Schaffarzick, 1952; Engleman, 1952). Kersley *et al.* (1953), studying 14 cases of rheumatoid arthritis treated with phenylbutazone, could find no change in uric acid excretion, although they noted sodium retention. On the other

hand, Smyth (1953) found a rise in the urinary excretion and a fall in plasma uric acid levels in a single case, and Bowers (1953) reported a death following phenylbutazone therapy in a gouty subject, in whom both ureters were found at necropsy to be blocked with uric acid crystals.

The published data on which these observations are based are relatively scanty, for opportunities of carrying out the necessary in-patient studies on patients with an essentially episodic disease are rare, especially if observations are needed during the interval rather than during the acute attack.

If phenylbutazone has a specific effect on uric acid metabolism and on acute gout this would be unique, for it would differ from that of other known drugs. Colchicine, which is effective in the acute attack, has no known effect on blood levels. The uricosuric drugs, such as salicylates, cinchophen, or probenecid ("benemid"), which lower blood levels by producing a uric acid diuresis, have never been found effective for the acute attack, apart from the analgesic effect of the first two. Probenecid, moreover, often precipitates an acute attack. Cortisone and A.C.T.H. have, of course, a uricosuric effect which is well documented (Thorn *et al.*, 1950; and many others), but this may be unrelated to their mode of action in relieving acute gout.

The suggestion that phenylbutazone lowers blood levels at the same time as it relieves the acute attack

conditions, and apart from its constant sodium-retaining effect (Green and Williams, 1953).

The following observations represent an attempt to throw some light on these possibilities by studying the effect of phenylbutazone on blood uric acid levels and urinary uric acid excretion at the same time in four cases of gout and one control patient.

Case 1

A man aged 63 had had episodic gout of six years' duration without formation of tophi. In addition, he had had three attacks of coronary thrombosis and there was evidence of renal impairment, his blood urea being 57 mg. per 100 ml.

TABLE I.—Means of Uric Acid Estimations on Case 1, Treated with Phenylbutazone 600 mg./day for 10 Days

Day	Vol. Urine (ml./24 hrs.)	Urinary Uric Acid (mg./24 hrs.)	Excess Urinary Uric Acid Excretion (mg./24 hrs.)	Blood Uric Acid (mg./100 ml.)	Phenylbutazone (mg./24 hrs.)
1-5	1,660	743	—	9.4	—
7-11	1,677	727	-16	4.3	600
12-16	1,761	1,056	+313	3.0	600

Total excess uric acid excreted days 7-16=1,485 mg.

and his urea clearance 48% of average normal function. His blood pressure was 180/100 mm. Hg. Unfortunately, he had an acute attack during the control period, during which the blood uric acid rose from 7.2 to 11.6 mg. per 100 ml. (Fig. 1).

On the seventh day of observation phenylbutazone, 600 mg. a day by mouth, was started. On the following day joint tenderness was much diminished, although whether this was due to the phenylbutazone or to the natural termination of the attack it was not possible to say. A sharp fall in blood uric acid levels was observed from 11.6 mg. on day 5, before treatment, to 4.3 mg. per 100 ml. on day 10 (Table I). During this period there seems to have been only a small excess excretion of uric acid, amounting to a total of 360 mg. only. This is just the sort of phenomenon described by some previous workers. During the second five days of treatment, however, there was a moderate diuresis of uric acid. During the first two days there was a slight diminution in water output, with a rise in urinary uric acid concentration from a pre-treatment mean of 45 mg. (maximum 53 mg.)

to a mean of 66 mg. per 100 ml., so that despite the fall in water output an actual excess of uric acid excretion occurred. During the second five days of treatment the mean urinary uric acid concentration was 62 mg. per 100 ml., and a total excess of uric acid excretion during the whole period of treatment, 10 days, amounted to 1,485 mg.

FIG. 1.—Chart of Case 1.

and that this is not accompanied by a comparable uricosuric effect deserves careful study. If this were true it might follow that phenylbutazone has some effect on uric acid metabolism itself. Such an effect, it must be recognized, would be coincidental to its mode of action in rheumatoid arthritis and other rheumatic

FIG. 2.—Chart of Case 2.

Case 2

This is a brief study of a man aged 52 giving a five-years history of episodes of acute gout occurring once a year until the previous year, during which he had had five attacks. He was admitted with a severe polyarticular attack in the big toe, both knees, and one elbow. Renal function showed a slight impairment, his blood urea being 34 mg. per 100 ml. and urea clearance 69% of average normal function. Urinary concentration was to a maximum specific gravity of 1020.

On admission his attack was beginning to subside, although the big-toe joint and elbow were extremely tender. Only one control day was available. His attack settled during treatment with phenylbutazone (Fig. 2), although the patient himself was unimpressed with the rate of subsidence and considered it to be at a normal rate. Some water retention occurred, the urinary volume being diminished from a control 1,570 ml. to 1,366 ml. per 24 hours (Table II). Urinary uric acid concentration rose from 34 mg.

TABLE II.—Means of Uric Acid Estimations in Case 2, Treated with Phenylbutazone 600 mg./day for Seven Days

Day	Vol. Urine (ml./24 hr.)	Urinary Uric Acid (mg./24 hr.)	Excess Urinary Uric Acid Excretion (mg./24 hr.)	Serum Uric Acid (mg./100 ml.)	Phenylbutazone (mg./24 hr.)
1	1,570	535	—	4.7	—
2-6	1,366	616	+81	4.2	600
7-8	1,495	668	+133	3.5	600

Total excess uric acid excreted days 2-8=671 mg.

to a mean of 45.2 mg. per 100 ml. (maximum 55 mg. per 100 ml.). The total excess of uric acid excreted during the first seven days amounted to 620 mg., and during this period the serum uric acid fell from 4.7 mg. to 3.5 mg. per 100 ml.

FIG. 3.—Chart of Case 3.

In this case, therefore, despite water retention, the increased concentration of urinary uric acid was sufficient to permit an excess of uric acid to be excreted.

Case 3

A man aged 76 had had attacks of gout for the previous fifteen years. No tophi had developed. During the control period there was an unsuccessful cystoscopy which was followed on the next day by an attack of gout. Again, the clinical response was satisfactory but not remarkable. There was a slight fall of plasma uric acid levels from 5.4 mg. per 100 ml. during the control period (three readings) to 5 mg. on the sixth day of treatment, and to 4.6 mg. on the day after completion of one week on phenylbutazone, 600 mg. a day (Fig. 3). A water diuresis occurred during the latter part of treatment and the urinary uric acid concentration rose from a mean of 47 mg. per 100 ml. (maximum 65 mg.) to a mean of 57 mg. (maximum 77 mg.) during treatment. The total excess of uric acid excreted amounted to 2,254 mg. (Table III). In this case, therefore, quite a marked uricosuric action is observed under conditions where water retention did not appear to occur.

TABLE III.—Means of Uric Acid Estimations in Case 3, Treated with Phenylbutazone 600 mg./day for Seven Days

Day	Vol. Urine (ml./24 hr.)	Urinary Uric Acid (mg./24 hr.)	Excess Urinary Uric Acid Excretion (mg./24 hr.)	Plasma Uric Acid (mg./100 ml.)	Phenylbutazone (mg./24 hr.)
1-7	1,291	580	—	5.4	—
8-14	1,631	902	+322	5.6	600
15-19	1,730	568	-12	4.8	—

Total excess uric acid excreted days 8-14=2,254 mg.

Case 4

This patient was a man aged 81 with severe chronic tophaceous gout. It was possible in this case to compare the action of phenylbutazone with a known uricosuric agent, probenidol. It can be seen from Fig. 4 that their actions were in this case somewhat different; phenylbutazone was followed by water retention, and the rise in the concentration of urinary uric acid was not quite sufficient to overcome this, so that although the concentration rose from 46 mg. to 79 mg. per 100 ml. (maximum 91 mg.), there was in

FIG. 4.—Chart of Case 4.

fact a net retention of uric acid amounting to 365 mg. At the same time, 2.7 litres of water was retained and the rate of urine output fell below 1 ml. a minute. This water retention became persistent, although the output returned to control values during probenidic administration (Table IV),

TABLE IV.—Means of Uric Acid Estimations in Case 4, Treated with Phenylbutazone 600 mg./day for Five Days and with Probenidic 2 g./day for Six Days

Day	Vol. Urine (ml./24 hr.)	Urinary Uric Acid (mg./24 hr.)	Excess Urinary Uric Acid Excretion (mg./24 hr.)	Plasma Uric Acid (mg./100 ml.)	Phenylbutazone (mg./24 hr.)	Probenidic (g./24 hr.)
1-9	1,069	483	—	7.9	—	—
10-14	524	410	-73	8.1	600	—
15-22	643	396	-87	7.2	—	—
23-28	998	580	+97	7.8	—	2

Total retention of uric acid during phenylbutazone therapy (days 10-14) = 365 mg. Total excess excretion of uric acid during probenidic therapy (days 23-28) = 582 mg.

and this, combined with an increased concentration of uric acid in the urine, allowed a net excess of uric acid amounting to 582 mg. to be excreted in six days, but a total water retention amounting to 6.5 litres appears to have occurred during the period of study. Ten days later the patient developed congestive heart failure; treatment with digoxin then led to a fall in weight from 10 st. 6 lb. to 8 st. 8 lb. (66.2 to 54.4 kg.), this being equivalent to 12 litres of water.

It can be well understood that body-fluid changes of this nature must influence plasma uric acid and urinary uric acid findings considerably, and must be taken into account. Great care is necessary before making any assumptions from investigations of this kind whether uric acid metabolism is being affected or whether the uricosuric action of phenylbutazone is sufficient to account for the changes observed.

Do non-gouty patients behave in a different manner from gouty patients? The main indication for phenylbutazone is pain unrelieved by aspirin, and, unfortunately, aspirin has a mild uricosuric effect, so that a pure picture is not readily obtainable from such cases. It has, however, been possible to study one patient in detail.

Case 5

This patient had Paget's disease, causing severe pain, which was relieved to a very real extent by phenylbutazone. Water retention did not occur here (Fig. 5; Table V), and there was a slight rise in the urinary acid concentration from a mean of 30 mg. per 100 ml. (maximum 35 mg.) to 34 mg. (maximum 42 mg.), and a small excess of uric acid was excreted with an associated drop in plasma uric acid levels. During the first week of phenylbutazone administration an excess of 686 mg. was excreted, the plasma uric acid falling from 4.9 to 2.6 and later to 2.3 mg. per 100 ml.

TABLE V.—Means of Uric Acid Estimations in Case 5 Treated with Phenylbutazone 600 mg./day for 16 Days

Day	Vol. Urine (ml./24 hr.)	Urinary Uric Acid (mg./24 hr.)	Excess Urinary Uric Acid Excretion (mg./24 hr.)	Plasma Uric Acid (mg./100 ml.)	Phenylbutazone (mg./24 hr.)
1-5	1,966	568	—	4.7	—
6-12	1,993	666	+98	3.3	600
13-21	2,454	628	+60	2.4	600
22-31	2,778	598	+30	3.2	—
32-35	2,505	760	+192	4.5	600

Total excess uric acid excreted days 6-21 = 1,226 mg.
Total excess uric acid excreted days 32-35 = 868 mg.

Discussion

These studies suggest that phenylbutazone has a fairly constant, if slight, uricosuric effect. In four of the five cases an excess of uric acid excretion occurred during the period of drug administration, and in the one case in which it did not occur water retention was enough to precipitate congestive heart failure following an observed retention of 6.5 litres of water. This effect, if it exists, is, however, insufficient to be demonstrable statistically on the data available. No advantage would seem to be offered by pursuing this aspect of the investigation further, although these observations would enable a suitable experiment to be designed to establish this.

Is it possible to assess whether in fact the fall in circulating uric acid level is greater than that which could be anticipated on the basis of excretion studies? If one assumes that the total body fluid equals 0.7 of body weight (Benedict *et al.*, 1950) and that uric acid is equally distributed throughout the body fluids, then it is possible to calcu-

FIG. 5.—Chart of Case 5.

TABLE VI.—Calculated Changes in Total Body Uric Acid Compared with Actual Excess Uric Acid Excreted During Phenylbutazone Administration

Case No.	Weight (kg.)	Body Water (litres)	Plasma Uric Acid (mg./100 ml.)	Total Body Urate Before Treatment (mg.)	Days Treated	Plasma Uric Acid After Treatment (mg./100 ml.)	Total Body Urate After Treatment (mg.)	Calculated Loss of Body Uric Acid (mg.)	Excess Uric Acid Excreted (mg.)	Discrepancy (mg.) (Urinary Excess — Calculated Change)
1	75.5	52.9	9.4*	4,973	6	3.0*	1,587	3,386	483	-2,903
2	70.0	49.0	4.9	2,401	6	3.5	1,715	686	620	-66
3	104.5	73.2	5.4	3,953	5	5.0	3,660	293	805	+512
5	57.3	40.1	4.7	1,885	14	2.3	922	963	1,050	+87

* Uric acid estimated in whole blood.

late from plasma uric acid readings before and after treatment the total loss of body uric acid and to correlate this calculation with the actual excess observed in the urine. Such a calculation is shown in Table VI. Case 4 is excluded, as measurements of actual body weight were not taken. Where more than one estimation of circulating uric acid was made before treatment the mean has been taken. Such calculations require certain assumptions which need not be discussed here. Nevertheless, if the falls in plasma levels were greater than could be accounted for by the excess excretion, clearly a consistent discrepancy would appear. In Cases 2 and 5 the discrepancy is small, and in Case 3 slightly more uric acid was excreted than can be accounted for by the fall in plasma levels.

Only in Case 1 is there the sort of discrepancy which would be required to claim that the fall in plasma levels is greater than can be accounted for by the excess excretion. It was in this case, however, that an acute attack developed during the control period, with a rapid rise in blood levels. The excess excretion of uric acid during this period is more than enough to account for the change in total blood uric acid. Calculating the plasma volume as 0.051 body weight, and assuming that the fall is due to clearance by the kidneys, it would require an excess excretion of 243 mg. to reduce the level from 9.4 to 3 mg. per 100 ml. In the event 483 mg. was excreted in excess during the relevant period.

Conclusions

There are thus two possible effects exerted by phenylbutazone and influencing uric acid estimations: (1) uricosuric—while this is no more than a mild effect it is nevertheless sufficient to account for the observed fall in circulating urate levels; and (2) water retaining—this was sufficient to precipitate congestive heart failure in the one case in which a uricosuric effect was not observed.

It is suggested that the variable preponderance of uricosuric and water-retaining effects would account for the variable findings. Much further evidence is required to establish still a third effect, on uric acid metabolism itself; and the fact that uric acid excretion may be increased when phenylbutazone is administered is against such a possibility.

Summary

Four cases of gout and one control case were treated with phenylbutazone and the changes in plasma uric acid and urinary uric acid levels were studied.

The findings suggest that phenylbutazone has no more than a slight uricosuric effect. This may be neutralized if considerable water retention occurs at the same time.

No evidence was found that phenylbutazone has any direct effect on uric acid metabolism.

Cases 1 and 2 were under the care of Dr. W. S. C. Copeman, to whom I wish to record my gratitude. I am also grateful to Dr. T. Simpson for allowing me to study Case 3.

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DEATH FROM HYPERSENSITIVITY DUE TO PHENYLBUTAZONE

BY

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Toxic effects of phenylbutazone have been described by a number of authors, and death has been ascribed mainly to agranulocytosis and to intestinal haemorrhage or perforation. A case is recorded in which death is attributed to a hypersensitivity reaction (in the course of phenylbutazone therapy).

Case Report

The patient was a man aged 73. Five years ago he began to have pain and stiffness in his hands and wrists. At first the pain was intermittent, but later it became continuous, until three years ago he had difficulty in moving his shoulders, elbows, wrists, and hands, and a diagnosis of rheumatoid arthritis was made. During the next year his knees and ankles were progressively affected. Two years ago he was unable to walk. He then received a course of gold injections, which produced little improvement, but was followed by a rash.

Nine months ago he was admitted to the London Hospital. Examination at that time showed a wasted, anaemic man, with classical rheumatoid arthritis. Ulnar deviation and spindling of the fingers, and swelling of the metacarpophalangeal joints, were present, with little movement of the wrists. Movement at the elbows and shoulders was painful and limited. His knees were swollen and his ankles painful and limited in movement. Other systems were normal, except that his pulse showed frequent extrasystoles, with a soft systolic murmur at the apex, probably not organic, but related to the anaemia. His blood pressure was 150/60. The erythrocyte sedimentation rate was 104 mm. in one hour; haemoglobin 69%; and leucocytes 8,700 per c.mm., with 74% polymorphonuclears. Rose's test was negative. He was treated by physical methods and with iron by mouth. After discharge, and five weeks before final admission, phenylbutazone was started, 0.2 g. twice daily by mouth. This produced a marked subjective improvement, so that he was able to walk a mile. After five weeks' treatment, however, his face began to swell, his eyes watered, and his mouth became dry and sore. He drank more fluids, but noticed that he passed scanty reddish-brown urine. He was short of breath, felt drowsy, and complained of a tingling sensation all over. Phenylbutazone was stopped, and he was admitted to hospital one week later.

Examination showed that his arthritis had undergone no striking change. He was rather confused and slightly flushed, with puffiness of the face. His tongue was dry and furred, and there were three tender ulcers on the inside of the lower lip, the largest 0.5 cm. in diameter. His pulse was regular, rate 120, and his blood pressure was 120/80. His apex beat was displaced outwards, and a third heart sound was heard at the apex but no murmurs. There were signs of fluid at both lung bases, and the liver was just palpable. The urine, which was orange-coloured, contained a cloud of albumin, and the deposit contained a few red cells and granular casts. An x-ray film of the chest showed cardiac enlargement, with hilar congestion and small bilateral pleural effusions, but the electrocardiogram showed only slight abnormalities—namely, ST depression in CR7. The leucocytes were 6,000 per c.mm. (polymorphonuclears 77%) and the blood urea was 38 mg. per 100 ml.

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