Occasional toxic effects are described. Some statistical considerations in the use of ranking methods are appended.

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FURTHER EXPERIENCE WITH AMIPHENAZOLE AND MORPHINE IN INTRACTABLE PAIN

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In a recent paper (Shaw and Shulman, 1955) it was shown that the combination of large doses of morphine (1–2½ gr., 65–160 mg.) with amiphenazole (D.A.P.T.; "daptazole") resulted in the alleviation of the intractable pain of terminal carcinoma. Since the publication of that paper the treatment has been used in further cases. The same total relief has been achieved in almost all the additional cases (127). Further evidence has accumulated that demonstrates the complete harmlessness of amiphenazole.

Present Series

Amiphenazole is one of a series of compounds which have been shown to arouse dogs deeply narcotized with morphine and hyoscine (Shaw and Bentley, 1955). In humans it counteracts the morphine-induced respiratory depression, vomiting, narcosis, and depression of the cough reflex without affecting the analgesia. The drug may also alleviate the constipation associated with the continued administration of morphine. We have observed the "pin-point" pupil of morphine in only one of our patients, although doses of 3½ gr. (217 mg.) have been given. Twenty patients have received large daily doses of morphine for periods of four to eight months without any evidence that tolerance has developed. In five cases it has been necessary to increase the dosage of morphine by 100%; in most instances the necessity for this increase could be accounted for by the increasing severity of the pain.

An unexpected outcome from the present series has been the bright mental outlook shown by three-quarters of these otherwise hopeless cases. Before treatment the subjects were all suffering moderate to severe pain and exhibited various degrees of depression. After about two weeks' treatment a remarkable change in the outlook of about 75% was noticeable. They took a renewed interest in the life of the ward, in occupational therapy, or in hobbies. Such a psychological improvement was noticed not only by the nursing staff but by the relatives.

It would, of course, be possible to ascribe these effects to the euphoric action of the morphine. The uplift did, however, markedly decrease when the patients still received morphine without the amiphenazole, and restitution of the amiphenazole after two weeks' deprivation again resulted in a mental improvement.

We feel that it can be said with some certainty that the improved mental outlook was due to the amiphenazole and not to the morphine, for the following reasons. When the use of amiphenazole was discontinued in the presence of large doses of morphine there was an interval of two to three days before depression and sleepiness set in. On restitution of the amiphenazole improvement in outlook took place within 24 hours. Several patients on 60 mg. of amiphenazole had to have their dosage reduced to 20 mg. because they had too much insight into their condition.

These findings of mild central stimulation provoked us to try the drug alone in cases of depression not associated with pain. The results showed remarkable promise. The series is, however, too small to enable one to draw conclusions. This work is proceeding and the results will be published later.

In the earlier paper (Shaw and Shulman, 1955) the possibility of toxic reactions from the use of amiphenazole was cautiously discussed. The main untoward feature was a mild untroublesome mental confusion in some of the aged patients. We were unable to decide whether to ascribe this to the large amounts of morphine or to the amiphenazole. It has not been observed in patients below the age of 55. The harmlessness of amiphenazole has been shown by the repeated administration of up to 300 mg. intravenously to healthy volunteers. This dose produces neither subjective symptoms nor any objective changes in blood pressure, heart rate, or respiration. (The usual therapeutic dose is 20–40 mg. orally.) We are indebted to Dr. Gershon for assistance in this matter. Chronic toxicity tests in animals are in progress, with, after four months, negative results. These tests are continuing.

Method of Treatment

Although in our series of over 127 cases we have not encountered a patient sensitive to morphine, we approach the use of large doses of that drug with caution. The patient will usually be receiving ½ or ¾ gr. (22 or 32 mg.) of morphine before treatment is started. The patient is then given doses of morphine which increase by increments of ¼ gr. (16 mg.) and 20–30 mg. of amiphenazole. It is permissible to mix the solutions in the one syringe, and the injections may be made intramuscularly or hypodermically. The injections are repeated when pain returns. The morphine increments are continued until the analgesia is complete for six to eight hours (it is not necessary to increase the dose of amiphenazole). The patient is then said to be stabilized. In cases of moderate pain stabilization will be reached with doses of 1–1½ gr. (65–95 mg.) of morphine (with 20–30 mg. of amiphenazole). Severe pain will require up to 3 gr. (195 mg.) of morphine at a single injection.

When the patient is stabilized (in about two days) the intramuscular injection of amiphenazole is replaced by oral administration. The oral dose will vary with the circumstances. As we have said, amiphenazole counteracts the sedative effect of morphine and may itself have a slight stimulant effect. Accordingly, in most patients it is possible to control the degree of alertness by increasing or decreasing the dose of amiphenazole given during the day. The range of oral dosage is 20–60 mg. In the evening and at night it is advisable to reduce the dose to 20 mg.

All our experience has shown that it is better to give a large dose of morphine than a small one. *There has been no evidence, in over 150 cases, of tolerance or addiction, so the patient should under no circumstances be denied the benefits of morphine.* The psychological advantage of never having the patient suffer pain cannot be stressed too much. It is well known that it is easier to prevent the onset of pain than to banish pain already in existence.

Only occasionally is it necessary to increase the dose of morphine above the stabilization dose during the course of the treatment. When the illness reaches the terminal stage it has often been found necessary even to double the dose of morphine during the last few days. It may also be advisable to decrease the dose of amiphenazole during this period if it is thought necessary to lessen the patient's insight into his condition.

It has been stressed that amiphenazole itself is harmless. Large doses of morphine in the aged may lead to harmless mental disorientation. There is only one indication for caution or cessation of treatment, and that is respiratory depression. This has been mildly encountered on only one occasion. It should be remembered that morphine depresses the metabolism so that the oxygen requirement is diminished. In a number of our cases the respiration has been depressed to 6-8 a minute. Although the breathing has been irregular it has been deep and signs of anoxia have never been observed. Acute respiratory depression due to morphine can be countered by intramuscular (or intravenous) injections of 20 mg. of amiphenazole at intervals of 10 minutes for a period of two hours. From our limited experience of amiphenazole as an antagonist to morphine-induced respiratory depression it would seem that the depth rather than the rate is increased. Amiphenazole has been found to exert no effect on the respiration if this is adequate.

Use of Other Drugs.—If sedation is required (especially at night) the patient may be given hyoscine—1/100 gr. (0.65 mg.)—or a short-acting barbiturate. Vomiting may be controlled with cyclizine ("marazine"), although mild emesis will usually yield to amiphenazole itself. Chlorpromazine has been used in several of our cases. It checks vomiting, but usually produces a profound depression which is not counteracted by amiphenazole, and we prefer not to use it.

The following case histories are typical of three cases, in order of increasing severity. Other results of the treatment are summarized in the Table.

Case 1

A pensioner, aged 59. Injury to his left shoulder in a fall from a bicycle, August, 1952. Developed lump in left axilla, with pain in shoulder following this. Also complained of pain and weakness in left arm. Biopsy of mass medial wall of left axilla: "fibrosarcoma." December, 1952: dissection of axillary gland field; at operation tumour shown to originate about insertion of latissimus dorsi, not from bone or periosteum. Some dyspnoea and pain in shoulder, but relatively well until May, 1954, when biopsy of gland from right inguinal region was done: report, "lymphosarcoma." Deep x-ray therapy: to axilla, June, 1954, total dosage 1,500 r in 18 days; to chest wall, total dosage 1,350 r in 18 days. Gradual deterioration till admitted to this hospital, December, 1954; severe pain in shoulder and arm. Chest x-ray showed infiltration of ribs locally under tumour mass with diffuse nodules throughout lung fields. Required morphine 1 gr. (65 mg.) (six-hourly); many complaints of pain about four hours after injection. On amiphenazole: a.m., 40-mg. doses; p.m., 20-mg. doses. Further course of therapy given with little change in size of masses in axilla. Injection of intercostal nerves with procaine, then alcohol, gave relief for only a few days. Steady increase in morphine dosage to 2½ gr. (170 mg.), with amiphenazole (a.m., 60-mg. doses; p.m., 20-mg. doses—six-hourly). With relief of pain patient became very euphoric; talked of going home as he was "cured though lumps still there." Amiphenazole reduced to 20 mg. six-hourly; after few days patient became drowsy and easier to manage.

Developed bronchopneumonia eight months after admission to hospital—at time of writing dying—no complaint of pain. Slight cyanosis. Respiratory rate, 12, deep and full. Drowsy and slightly disorientated.

Case 2

A saleswoman aged 41. On admission to this hospital (December, 1954) gross cachexia, anorexia, fluids only, continual complaint of pain in back and right leg (sciatic distribution) in spite of injections of morphine ½ gr. (11 mg.) p.r.n.—usually two-hourly. Morphine increased to ½ gr. (32 mg.) six-hourly with amiphenazole 20 mg. (oral). Injection of intrathecal alcohol (0.5 ml.) gave no relief. Blood examination: Hb, 6.6 g./100 ml. (44%). Given 2 litres of blood (O₄, Rh positive) in hope that increased haemoglobin might bring some improvement. General condition improved but pain unrelieved, and with increasing dosage of morphine patient became drowsy, nauseated, and vomited food. Amiphenazole, increased to 40 mg. (oral) six-hourly, with morphine 1½ gr. (100 mg.), still left patient nauseated, restless, and unable to sleep. Changed to amiphenazole, 60 mg. (oral) with a.m. doses and 20 mg. (oral) with p.m. doses. The relief of pain was now almost complete. In her last three weeks of life morphine was increased up to 2½ gr. (150 mg.) six-hourly, with patient very alert, pain-free, and talking about going home, as pain was no longer present. Requested hairdresser and cosmetics, which she used regularly in effort to improve her appearance. It was felt that more sedation was necessary at this stage, so amiphenazole was reduced to 20 mg. (oral) six-hourly, and patient remained comfortable, pain-free, and drowsy, though able to eat and mentally clear. Died April, 1955. P.M.: Carcinoma of rectum—local recurrence—metastatic carcinoma of the liver.

Case 3

A housewife aged 71. Well and active till November, 1954, when she complained of gradual onset of pain between shoulders and in right loin extending across back to left side, continual but not progressive—thought to be cholelithiasis. March, 1955—legs suddenly became weak and patient unable to walk and, after two days, to stand on legs. Admitted to hospital—paraplegic, pain in left loin, sacral bed sore, incontinent of urine, faecal impaction.

X-ray film, March, 1955: Destruction and compression of eleventh dorsal vertebra with paravertebral soft tissue mass on right side. Elsewhere generalized osteoporosis.

Blood examination: Hb, 11.3 g. per 100 ml. (76%); leucocytes, 6,000 per c.mm. (neutrophils 86%, lymphocytes 12%, monocytes 1%, eosinophils 1%); platelets normal.

Marrow biopsy (sternal and iliac crest): Myeloid and erythroid elements normal; 5% plasma cells, many abnormal in general nature.

In conjunction with x-ray findings—diagnosis of multiple (plasma-cell) myeloma. Given course of deep x-ray therapy to spine (dorsal). Total dosage, 2,000 r in 21 days. Pain was at all times severe since admission to hospital, and after initial dosage of morphine ½ gr. (32 mg.) with amiphenazole 20 mg. (oral), increase was necessary frequently, as relief was obtained only for periods varying from two to four hours after injection. Eventually stabilized and pain-free on morphine 2½ gr. (170 mg.), with amiphenazole 20 mg. (oral) six-hourly, three months after starting on regular morphine dosage. Developed sinuses over both hips, which were irrigated and dressed four-hourly, and infected x-ray burn over dorsal spine; chemotherapy given according to sensitivity; nursed on "rotobed." Increasing pain necessitated increase in morphine 3 gr. (195 mg.) (six-hourly), amiphenazole 20 mg., given by injection as patient was unable to swallow tablets. With relief of pain patient was bright, would read papers, and took an interest in ward procedure. This dosage continued for three weeks, but condition gradually deteriorated—terminal disorientation and coma. Died four months after admission to hospital. P.M.: Carcinoma of kidney (left), metastatic carcinoma of vertebrae D 10 and D 11.

Results of Treatment in 15 Cases

Age and Sex	Stabilization Dose of Morphine (mg.)	Amount to which Dose had to be Increased before Terminal Stage Morphine (mg.)	Dose of Amiphenazole (mg.)		Duration
			a.m.	p.m.	
53 M	15		20	20	6 months
45 M	30	60	20	20	6 "
66 M	45	80	60	20	3 weeks
67 M	90	100	20	20	
55 M	15	32	20	20	
39 M	12	22	20	20	
51 F	15		20	20	3 months
73 F	12		20	20	5 "
50 F	15	90	20	20	3 "
58 F	15	32	20	20	
79 F	15	65	20	20	2½ "
56 F	32	66	40	20	1 month
37 F	15	22	40	20	3 months
62 F	32	32	30	20	6 "
54 F	15	65	60	20	

It is concluded that the advantages to be gained from the use of amiphenazole with large doses of morphine in the treatment of intractable pain are: the ability to control the pain from the beginning, the induction of a bright mental outlook in the patient, and the possibility of using large doses of morphine for at least six months without the development of any marked tolerance.

Summary

The treatment of 127 cases of intractable pain in terminal carcinoma is described. Complete abolition of pain was obtained for 24 hours by the use of large doses of morphine (1–3 gr., 65–195 mg.) and a new drug, amiphenazole. The mixture was given three or four times a day for periods of up to eight months. The main advantages of the combination are as follows. Administration of large amounts of morphine without respiratory depression, narcosis, or depression of the cough reflex; amiphenazole apparently prevents the onset of any marked tolerance to morphine, and possesses a central nervous stimulant action of the caffeine type; and treated patients have a bright mental outlook under otherwise hopeless conditions.

We thank Dr. T. B. Patrick, medical superintendent of the Austin Hospital, and Dr. W. Holman, Director of the Peter MacCallum Cancer Clinic, for facilities to carry out this clinical trial and for the interest they have shown. We also thank those resident medical officers who have contributed to this project, and Dr. Kaye Scott, whose interest and help have been of the greatest encouragement to us. Generous gifts of drugs were made by Drug Houses of Australia and Nicholas Pty. Ltd. Part of the expenses were defrayed by a grant from the National Health and Medical Research Council of Australia.

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"I am of the decided opinion that unless a complete reorganization of the public analyst service of this country is undertaken in the near future, it will eventually die of anaemia. Its laboratory facilities, its staffing, and the manner in which the all-important sampling is carried out are all out of date and quite unable to cope with modern conditions. The country is split up into far too many food and drug authorities, resulting in the duplication of effort, in the narrowing of the field of work, and in the expenditure of money which could be better employed in more useful ways than the traditional ones."—*City of Birmingham: Annual Report of the City Analyst for the Year 1954*, December, 1955. Of 5,847 samples of food and drugs examined by the Birmingham city analyst's department in 1955, 481 (7.6%) are stated to have been adulterated, below standard, of inferior quality, or incorrectly labelled.

ATRESIA OF THE ABDOMINAL AORTA

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Occlusion of the abdominal aorta by thrombus, a relatively common condition, has been reviewed in detail by Burt *et al.* (1952). Though the following case may fall into this category, the finding at operation of atresia of the aorta and of the common iliac vessels with healthy walls makes it worth recording because of the possibility that it is of congenital origin.

Case History

A butcher aged 47 complained of an ulcer on the second right toe that failed to heal in spite of treatment. He also complained of pain in both calves during effort. Both conditions had been present for some months.

On further questioning, he admitted that for five years he had had some trouble in his calves during exercise. He also admitted having rest pain in the feet at night which was relieved by getting up. The feet were always cold and white. The ulcer first appeared ten months before admission, was very painful, and resisted treatment with anticoagulants, "hydergine," tolazoline hydrochloride, and antibiotics. His "claudication distance" shortly before admission had come down to 10 yards. The past history and family history contained little that was relevant to the present complaints. He was rejected for military service in 1941, but was given no definite reason for this. His father died of dropsy at the age of 71, his mother of gangrene at 80.

The patient was well developed and of good colour. The blood pressure in each arm was 140/109 mm. Hg. No readings were possible in the legs. The radial pulse was 110 regular, and well sustained. There was no cyanosis. The apex beat was in the fifth interspace in the M.C.L. Heart sounds were closed. All arm pulses were present. However, no aortic pulse was palpable in the abdomen and no pulses were present in the region of the external iliac, femoral popliteal, dorsalis pedis, or posterior tibial arteries in either limb. The left foot was pale and rather cold. The right was warmer but showed cyanosis of the toes. A hard black crust was present on the pulp of the second right toe. Venous filling was poor. There was no oedema or telangiectasis. Oscillometry gave no recordable readings in either thigh or calf at levels of from 180 to 80 mm. Hg. After heating the trunk and arms with an electric blanket there was a limited rise of temperature in each foot. It was found impossible to needle the abdominal aorta by the percutaneous lumbar route for reasons which appear obvious in the operative note.

As a result of these investigations a provisional diagnosis of aortic thrombosis was made. In view of the ischaemia of the feet, of the relative youth of the patient, and of the positive skin temperature reaction, a decision to carry out bilateral lumbar sympathectomy was made.

The lumbar chain was approached by the anterior extra-peritoneal route through a horizontal incision at the level of the umbilicus. During the course of the operation on the left side the opportunity was taken of exploring the aorta. The following condition was found. At the level of the renal vessels the aorta terminated in a bulbous pulsatile cul-de-sac. Below this a narrow pliable tube about the size of a pencil (0.5 cm.) passed down to a normally situated bifurcation from which two narrow common iliac