THE TREATMENT OF INTRACTABLE PAIN*

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The rapid increase in medical knowledge which has taken place during this century has brought with it not only specific forms of treatment, but also a clearer appreciation of the physiological and pathological states with which we are confronted. Symptomatic as well as specific treatment has therefore benefited and become more rational and effective. In fact almost every advance in medicine has had some bearing, direct or indirect, on our management of the common and urgent symptom of pain.

My intention in this article is to discuss the effect of hormones, with or without cytotactic drugs, some aspects of deep X-ray therapy, and the adjuvant action on morphia or its substitutes of some recently available drugs, in certain conditions where pain dominates the clinical picture.

THE STEROID HORMONES

All will agree that the steroid hormones, with their powerful and widespread effects, should be used as pain killers on rare occasions, and then only when the therapeutic problem is clearly understood. There are, however, circumstances when their use as a pain killer is justified.

The condition for which the adrenal steroid hormones were first widely used gives us an example, as the severity of the pain in acute rheumatoid arthritis may well enforce the temporary use of cortisone in the full knowledge that its analgesic effect must be paid for by the troubles of withdrawal, and possibly the development of side-effects.

Gout is another example of a cortisone-like substance being welcomed simply for the control of pain which it affords when other measures have failed. Its use will be purely symptomatic as it will have no curative effect, and in fact will produce a relapse when it is withdrawn. The relief of pain may, nevertheless, be quite dramatic, and relapse can be prevented by continuing with colchicine after stopping the cortisone.

A less well known example of pain controlled by steroid hormones is provided by cranial arteritis, in which the pain may be both severe and baffling from the diagnostic point of view. The vertical, temporal or occipital pain of a persistent character about which an elderly patient may complain with an intensity which compels attention is familiar in this condition, but a paroxysmal pain is more unusual.

A man of 72 was recently seen complaining that for a month he had an agonizing pain starting behind the right eye and spreading to the right side of the forehead and cheek. The pain was of great intensity, lasting 30 to 45 minutes, and was burning in character. There were no abnormal physical signs and he was a poor witness but his story had a genuine ring, and he insisted that the pain was produced when he got his head into a certain position. He demonstrated this by lying back on his pillows with his face turned to the right, and at once jumped up in obvious agony.

Many diagnoses were considered, including the correct one, but this was only firmly established when tenderness and thickening of the right temporal artery appeared at the same time as he experienced partial loss of vision in the eye on that side. Cortisone entirely relieved his pain and he has made an excellent recovery apart from the partial loss of vision. Before reaching the correct diagnosis his outlook appeared to be bad, for his pain was agonizing and uncontrolled without large doses of powerful analgesics.

STEROID HORMONES AND CYTOTACTIC DRUGS

The steroid hormones and corticotrophin, in combination with alkylating agents, may be effective in temporarily controlling pain from widespread metastases, including those in the liver and lungs. This form of treatment is worth considering in a patient suffering from an advanced stage of carcinomatosis when the primary growth is pancreatic, gastric, renal or colonic. It can also be tried for widespread secondaries from the breast or prostate when gonadectomy and sex hormone treatment have been used and their effect is waning. Steroid hormones and cytotactic drugs should

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however be used with caution when moniliasis is present or develops in already debilitated patients.

Triethylene melamine is an alkylating cytotactic drug which can be taken by mouth. A total of 0·1 to 0·2 mg. per kg. is given in divided doses over a three-day period, and may be combined with 40 units of corticotrophin gel, which should be given twice daily for a few days before and during the treatment.

Nitrogen mustard in similar dosage and combination with corticotrophin can be given by injection. A convenient means of doing this is to inject it into a fast running intravenous drip of 5% glucose, in three doses at intervals of 48 hours.

The value of the adrenal steroids may be that they supplement the lympholytic action of the nitrogen mustard, and they may also have a protective action upon the blood-forming organs (Lemon, 1956). The latter is of great importance, as the possibility of using this form of treatment depends on reasonably normal activity of the bone marrow, with adequate leucocyte and thrombocyte production. It can therefore only be carried out with reasonable safety when adequate haematological control is available. The period of relief achieved may not be more than one or two months, but that may be sufficient to spare the patient severe pain up to the time of his death.

Adequate haematological control is also obviously of first importance when patients with a reticulosis such as Hodgkin's disease or follicular lymphoma are undergoing treatment with some form of mustard preparation.

Gross discomfort is commoner than severe pain in the reticuloses, but the distinction may be a fine one, and valuable relief may be obtained by reducing local pressure. This is usually done by deep X-irradiation, but chemotherapy may be of some value when the apparatus is not readily available, or when a patient already far advanced in disease wishes particularly to remain in or near to his own home. Chemotherapy also has a part to play when large local skin doses of deep X-rays have already been given.

Triethylene thiophosphoramide, or Thiotepa, is a useful mustard preparation in the reticuloses as it can be given by mouth or by the intravenous or intramuscular route and is not locally irritating. An initial dose of 5 mg. by injection on alternate days, or 10 mg. by mouth daily, is adjusted by the response of the blood count, which should at first be estimated daily. The total amount given in a course will vary according to the blood count between the approximate limits of 75-225 mg. and may be preceded or accompanied by a steroid hormone, such as prednisolone, 10 mg. three times a day.

Very severe pruritus can occur in Hodgkin's and allied diseases, and be both intensely distressing and exhausting to the patient. It may, however, respond to antihistamines and steroid hormones in combination, and this is a real advance in symptomatic treatment.

ANTIMETABOLITE DRUGS

As in the reticuloses, pain is not a particularly common symptom in the leukaemias, but at times the misery from the condition of the mouth in acute leukaemia may be almost unendurable. It is then that the only real relief, albeit temporary, may be from some antimetabolite drug, with or without corticotrophin or cortisone. The most useful of these drugs at present is 6-mercaptopurine, an antipurine antimetabolite with practically no toxicity (Galton, 1957). It is given in initial daily doses of 2·5 mg. per kg., the subsequent dosage being controlled by the white blood and platelet counts. In practice the treatment has to be continued until the marrow is aplastic if it is to have any hope of producing a real effect.

Corticotrophin or cortisone can be given with the 6-mercaptopurine, and are especially necessary as the marrow becomes increasingly hypoplastic.

Amethopterin, a folic acid antagonist, is the most useful drug in children, but will itself cause severe ulceration of buccal mucosa and the gums. It does not, therefore, give symptomatic relief quickly, but in conjunction with the steroid hormones may lead to remission of the leukaemic state for several months.

The spleen in chronic myeloid leukaemia is occasionally a source of great discomfort, or even of severe pain if perisplenitis develops and persists. Once again deep X-irradiation is the treatment of choice, but Busulphan (Myleran) in 2 mg. doses, three times a day, continued until relief is achieved or the white blood count falls to a normal level, can be used in the patient's home with all the attendant advantages in the way of maintaining morale and some sense of happiness.

THE SEX HORMONES

Gonadectomy has long been practised for the relief of metastases, chiefly in bone, when the primary growth is in the breast or the prostate gland, and further value was added to this procedure when the oestrogens and testosterone came into use. The control of the extragonadal secretion of sex hormones is the object, and since the advent of cortisone as replacement therapy, adrenalectomy and hypophysectomy have become possible and on occasions are effective means of achieving this. It is usual to begin the treatment by using sex hormone therapy alone. Oestrogen, in the form of stilboestrol, or chlorotrianisene (Tace), is used in the case of cancer of the prostate, and testosterone for cancer of the breast. Eventually, however, tolerance is acquired and gonadectomy has to be considered. This relatively simple procedure, together with sex hormone administration, may result in a further period of remission, but if this combination fails or relief is short-lived, the difficult decision about further operative treatment must be faced unless some alternative can be found.

A possible alternative is at present under trial at various centres and consists of destruction of the pituitary gland surgically or by an implantation of radio-active gold or yttrium. Mr. Geoffrey Bateman has kindly given me permission to report the results he has so far obtained at St. Thomas's Hospital.

His surgical approach to the pituitary fossa is trans-septal. Sub-mucous resection of the nasal septum is carried out and the sphenoidal sinus is opened. The septum dividing the cavity into two is removed and the downward bulge of the pituitary fossa identified in the roof of the cavity. A probe is introduced against this bulge at an angle previously determined by radiographs, and its exact position established with the help of an X-ray image intensifier. The floor of the pituitary fossa is then punctured at this point and a seed or seeds of the radio-active element implanted.

Optic atrophy has recently been observed following the use of radon seeds or radio-active gold grains in the pituitary, and it is in an attempt to avoid this that radio-active form of the element yttrium has come into use. Yttrium (^{90}Yt) has a short half-life (61 hours), similar to that of radio-active gold, but unlike ^{198}Au its emanations are pure beta rays with an intense local reaction. Radio-active gold, on the other hand, has both gamma and beta irradiations, and it is the former which prove a hazard to the optic chiasma. Mr. Bateman has done a trans-septal hypophysectomy on 12 patients with secondary deposits from carcinoma of the breast. Four of these showed improvement and 8 no improvement. His figures for radio-active gold implantation are similar, namely 11 cases, of which 4 were improved and 7 not improved.

At the time when this paper was completed he had implanted yttrium into the pituitary of 3 patients, 2 of whom had improved and 1 had not improved. One of the two cases showed an improvement sufficiently striking to deserve special mention. Professor J. B. Kinmonth, who suggested to Mr. Bateman that he should develop this work, has kindly given permission for this.

Mrs. M., aged 47, was admitted to St. Thomas's Hospital under the care of Professor J. B. Kinmonth on 18 March 1957, with a stage 4 carcinoma of the right breast. She had noted a lump 3 years before and it had slowly enlarged. For 8 months the right nipple had been ulcerated and for 3 months she had had a cough with some sputum and had been short of breath.

On examination she had a hard mass in the right breast behind the nipple, which was affected by Paget's disease (Fig. 1). The mass was fixed to the skin and to the deep tissues, and there were secondary glands on the right side of the neck and one fixed in the right axilla. The X-ray of her chest showed extensive secondary deposits in both lung fields (Fig. 5a). There were no bony deposits demonstrable radiographically.

Mr. Bateman implanted 4 yttrium pellets, using the technique I have mentioned (Figs. 3 and 4). An effect on the pituitary was demonstrated by radio-active iodine studies, which showed a thyroid uptake of 55% before operation, and only 5·6% after the operation. The patient also developed vomiting and a fall in blood pressure 20 days post-operatively.

Fourteen days after the operation (17 April 1957) the primary growth was half its original size (Fig. 2), the fixed axillary gland had gone and the ulceration of the nipple had healed (Fig. 5b). All the glands in the neck had disappeared except for one which was half its original size. X-rays of chest showed marked improvement, all the secondaries being smaller (Fig. 5b).

She was discharged on 7 May with further improvement in the chest X-ray appearances, taking 25 mg. of cortisone twice a day.

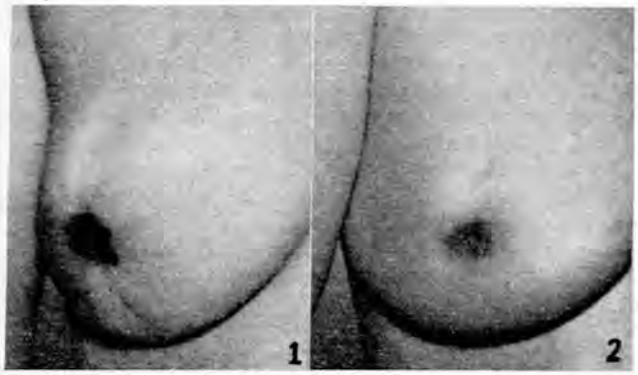
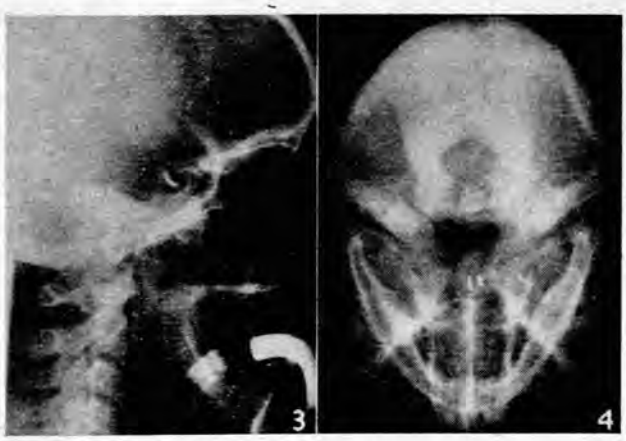


Fig. 1. Carcinoma of breast before treatment.
Fig. 2. Same case after treatment.



Figs. 3 *and* 4. Yttrium seeds in position.

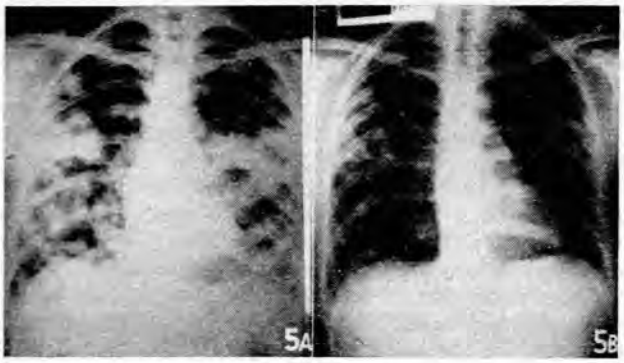


Fig. 5*a*. X-ray of chest before treatment.
Fig. 5*b*. X-ray of chest after treatment.

On 3 June, 2 months after operation, no glands were palpable, no mass was found in the breast, the nipple had healed and she was gaining weight. She had, however, a little trouble from diabetes insipidus.

This is only a single case of treatment with ^{90}Yt, but the result so far is remarkable.

Another alternative to radical surgery is presented by the possibility of suppressing pituitary and adrenal function by the use of cortisone. This method is better adapted to dealing with metastases from the breast than from the prostate, as cortisone is partly metabolized to androgens and thus supplies an unwanted hormonal stimulus to secondaries from a prostate growth, whereas its products have no oestrogenic activity. Lemon (1956) reports from his clinic that so far the results of treating patients with carcinoma of the breast with pituitary and adrenal suppression by cortisone in women who have been castrated are not significantly different from the results he has observed from hypophysectomy or adrenalectomy. He advocates the use of dried thyroid extract in the belief that this acts synergistically with cortisone in helping to reduce pain from secondary deposits in bone from the breast. He thinks the dried thyroid may also help the process of recalcification and repair (Lemon and Reynolds, 1956).

The dosage of cortisone must be of the order of 100 mg. daily or, if it is given as prednisolone, 20-25 mg. a day. Lemon's regime is therefore gonadectomy (it is unnecessary to remove the ovaries in women over 70 years of age), methyl

testosterone by mouth, 30-80 mg. a day, or propyl testosterone, 50 mg. three times a week by injection, cortisone, 100 mg., or prednisolone, 20 mg. daily, and, in addition, 30-100 mg. of dried thyroid extract.

DEEP X-IRRADIATION

Irradiation of normal nervous tissue will not, in therapeutic dosage, either diminish or abolish painful nervous stimuli (Fleming, 1957). Central irradiation of the brain and spinal cord within safe limits for, for instance, cerebral and spinal-cord tumours, does not show any immediate effect upon the normal function of sensory or motor pathways. Heavy irradiation within the therapeutic range has, however, been known to cause, after a delay, gliosis in the brain and spinal cord, with clinical manifestations such as paraplegia. It is thought that this is due in large part to vascular ischaemia produced in the connective tissue rather than to direct action upon nerve cells and fibres. Relief of pain from radiotherapy is therefore, as in the case of cytotactic drugs, achieved usually by an indirect effect through its action on underlying diseased tissues.

This is illustrated in the treatment of carcinoma of the bronchus, where great symptomatic relief can be obtained in some carefully selected instances where pressure on surrounding structures has occurred. If, however, the tumour is apical, the so-called Pancoast tumour, irradiation, which necessarily involves the brachial plexus, will produce little or no relief of pain in the shoulder and arm.

Deep X-irradiation is of great value in controlling pain from some metastatic deposits in bone, particularly from the breast, or from invasion of bone by reticulo-sarcoma. It will control pain from such highly radio-sensitive abdominal tumours as lympho-sarcoma and seminoma. The successful eradication of many early growths by irradiation in such sites as the mouth and throat, skin, anus, vagina and bladder is often achieved with relief of accompanying painful symptoms. Headaches from both primary and secondary cerebral neoplasms may also be much relieved, a point worth remembering even when the outlook is hopeless.

Among the painful conditions in which radiotherapy may give symptomatic relief, mention must be made of Paget's disease of bone when the pain is reasonably localized, ankylosing spondylitis, acute subacromial bursitis and tendinitis, and the frozen-shoulder syndrome. An interesting example of the control of pain of inflammatory origin is provided by irradiation of the parotid gland in the early stages of acute parotitis. This may be of considerable practical importance if acute parotitis occurs when a patient is in a severely debilitated state.

ANALGESIC DRUGS

Concurrently or subsequently to the use of other methods, analgesic drugs will inevitably play some part in the treatment of chronic pain, and although we are still very largely dependent upon long-established analgesics there have been recently some advances in the manner in which they are used.

The value of mild analgesics is sometimes greater than is universally realized and is a point which has been supported on a more scientific basis by the interesting work of Beecher (1953), who showed that 10 gr. of acetylsalicylic acid was demonstrably more effective as an analgesic than 1/6 gr. of morphia or 1 gr. of codeine, all by mouth.

Beecher (1956) has also shown that placebos can have an effect on pain of undoubtedly organic origin, and that the significance to the patient of the lesion producing the pain can block or determine the pain experience.

The significance of a pain varies enormously, and it may even become so accustomed or protective that it is necessary to the patient, as Penman (1954) has shown in the case of trigeminal neuralgia.

The relief of anxiety by sensible discussion and possibly by the use of sedatives has long been a first step in the management of chronic pain. To this end chlorpromazine has been used in clinical practice for some time. There are many patients dying with malignant disease in whom resort to morphia can be delayed until the last hours of life, or even avoided altogether by its use. Chlorpromazine has no analgesic action of its own, but seems to potentiate that of narcotic drugs, as well as having its special effect of reducing the patient's emotional response.

It is the experience of most that large doses of chlorpromazine are required, and that the drug is far more potent by injection than by mouth. Gordon and Campbell (1956) gave it by mouth in 25 mg. doses four times in the day, with 50 mg. at night, thus making a total of approximately 150 mg. in 24 hours. They followed up, for a period of 1 to 18 months, 32 patients so treated who had intractable pain from carcinomatosis. They found no toxic effects from the drug beyond some drowsiness in elderly patients, and concluded that chlorpromazine is a useful adjuvant in the control of persistent pain. They observed an almost invariable reduction in the quantity of analgesic required. The mental outlook of their patients improved and, without exception, they ate and slept better when they were taking chlorpromazine.

When more powerful analgesia is required, i.e., in the control of pain from a coronary thrombosis, morphia or a substitute will be required. It is not proposed to discuss the numerous morphia substitutes which are now available, but merely to mention that methorphinan (Dromoran) is regarded by many experienced practitioners as particularly useful as it can be given effectively by mouth. It is also thought to be less habit-forming than morphia, and most women are less nauseated by Dromoran, pethidine (Demerol), or amidone hydrochloride (Physeptone), than by morphia. Nevertheless, all these drugs tend to produce some nausea unless the patient is more or less confined to bed.

The respiratory depression which is produced by morphine, pethidine and Dromoran can, it is claimed, be reduced by levallorphan tartrate in approximately 0·5-1·5 mg. doses but its effect on tolerance, addiction, nausea and constipation have not yet been fully worked out.

Another possible method of increasing the effectiveness of morphia and of diminishing its ill effects in the control of intractable pain in the terminal stages is its combination with amiphenazole (Daptazol), as described by Shaw and Shulman (1955). Further experience of this treatment in 127 patients has been reported by McKeogh and Shaw (1956). They found that even a very large dose of morphia, 55-160 mg. (grains 1-2½), when combined with 20 to 30 mg. of amiphenazole in the same syringe, was not followed by respiratory depression, narcosis or reduction in the cough reflex. They believe that, in addition, amiphenazole

retards the development of tolerance and has a caffeine-like effect, with a brightening of the patient's mental outlook. This method is clearly worthy of further trial, not only to permit large doses of morphia to be given when they are necessary, but also in the hope of making a smaller dose more effective than would have been possible without the addition of the Daptazol.

Apart from the use of combinations of newly synthesized drugs, numerous measures have been devised for the control of chronic pain, notably by neurologists. Such a method is the injection of the interspinous ligaments with local anaesthetic (Fischer-Williams, 1956). Anaesthetists also are interested in the control of intractable pain, and use their skill by injecting alcohol intrathecally or by blocking nerves. Surgeons have for many years done operations such as cordotomy and have more recently, in cooperation with psychiatrists, reduced the disadvantages and increased the advantages of leucotomy.

When all other measures have been exhausted and the nature of the situation is such that pain will persist until the patient's death, morphia or its substitute will often have to be given to the end. It is not, however, always necessary to resort to injections immediately and thus abandon the great advantages of oral medication. Whatever preparation or method of administration is chosen, it is sometimes wise to prescribe it at definite intervals throughout the day. The length of these intervals will be determined with the object of preventing the development of agonizing pain but not necessarily of abolishing pain entirely. If this is not done severe clouding of consciousness may alternate with periods of agony, or the patient may linger on interminably, to the distress of those who love him.

I feel we should try to avoid these things so that our patients may die with all possible dignity as well as in peace.

It is a pleasure to thank Mr. G. H. Bateman, Prof. J. B. Kinmonth and Dr. J. A. C. Fleming, all of St. Thomas's Hospital, London, for their kindness in allowing me to refer to their work.

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