who used short intermittent courses of salicylate, in contrast to our continuous intensive and controlled therapy. In all other respects the two series are comparable, and, like Ernstene (1930), we had a small number of "polycyclic" cases which promptly relapsed after salicylate was discontinued. This happened in six of our patients, and each relapse was accompanied by elevation of the plasma fibrinogen, which reverted to normal after a second course of aspirin.

One of the patients developed a second similar relapse, and the findings are shown in Fig. 2, where it will be observed that discontinuation of salicylate was followed by clinical relapse and simultaneous elevation of plasma fibrinogen; these changes were immediately reversed when aspirin was started again. It is also noteworthy that in this case two parenteral courses of penicillin, in which 0.6 million units and 1.2 million units daily were started 12 and 7 days respectively before the first and second relapses, were not effective in preventing relapses.

Discussion

The plasma fibrinogen concentration in acute rheumatic fever treated with full doses of aspirin has been found to fall rapidly and uniformly in a series of 33 cases. Comparison of the present results with those of Ernstene (1930) emphasizes these features of our results: the mean plasma fibrinogen of his best, "monocyclic," subgroup did not reach 0.4 g. per 100 ml. till the fourth week of treatment; the corresponding time for *all* the present cases was two weeks. Even more striking in the present series is the lack of increasing scatter in the plasma fibrinogen concentration with the passage of time. This finding is difficult to reconcile with the view that salicylate only relieves the symptoms of rheumatic fever, and is impossible to interpret in relation to the careful study of Ernstene (1930) without inferring that an intensive and continuous course of salicylate does indeed, within three weeks, consistently lead to a rapid reduction in the plasma fibrinogen concentration in acute rheumatic fever.

Certain practical implications arise from the present study. Since hyperfibrinogenaemia is an essential feature of rheumatic fever (Fig. 1(a)), (1) the plasma fibrinogen concentration may be a reliable index of the course of the disease, and (2) sufficient salicylate, given for an adequate time, can restore the plasma fibrinogen to normal, and presumably arrest the rheumatic process, without necessarily influencing the chain of events leading to the elevation of the plasma fibrinogen concentration.

Above all, the present results provide definite evidence that salicylate does more than relieve symptoms. Even after 21 days' treatment seven of our cases showed fibrinogen levels which, although reduced, were still slightly abnormal; this confirms that there is no set optimum dosage schedule of the drug, and that in each case dosage and duration of therapy must be controlled not only by frequent serum salicylate estimations but also with reference to the fibrinogen concentration or some comparable index of rheumatic activity.

The connexion between plasma fibrinogen and the characteristic clinical and pathological features of rheumatic fever is being investigated further.

Summary

The abnormally high plasma fibrinogen concentrations found on admission to hospital in 33 patients with acute rheumatic fever fell rapidly and uniformly during a continuous intensive course of aspirin, controlled by serum salicylate estimations. This clearly demonstrates the advantage of proper aspirin therapy.

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SUPERFICIAL MALIGNANT LESIONS OF BLADDER TREATED BY RADIOACTIVE COLLOIDAL GOLD (^{198}Au)

BY

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In the treatment of multiple superficial lesions of the bladder intracavitary irradiation has a distinct advantage over external deep x-ray therapy because it protects adjacent healthy organs. Several techniques have been developed for the use of gamma-radiation-emitting radioactive substances as an intravesical source of irradiation (Friedman and Lewis, 1949; Becker and Scheer, 1952; Schulte, Hinman, and Low-Beer, 1952; Walton and Sinclair, 1952). The disadvantage of penetrating gamma-radiation, however, is the development of secondary cystitis and a risk of fibrosis with impaired function of the bladder.

For very superficial lesions it seemed possible to use beta-radiation. Because the dose of beta-emission falls rapidly at depth the best method is the instillation of a radioactive solution direct into the bladder in order to get the emitting substance into close contact with the bladder mucosa and to surround the papillomatous villi by the radioactive material. Ellis and Oliver (1955) used radioactive gold (^{198}Au) in this way. Einhorn, Larsson, and Ragnhult (1955) suggest the use of radioactive yttrium (^{90}Y), and Walinder (1955) colloidal $^{76}\text{As}_2\text{S}_3$ for the purpose.

Radioactive colloidal gold is suitable for this method because of its half-life, its type of emission, and its colloidal nature. Since the half-life is short (2.7 days), there will be no danger of contamination after a few days. It emits about 95% of beta-radiation with 0.96 MeV energy, and 5% of gamma-radiation with 0.41 MeV energy. The maximal penetration of its beta-particles in soft tissue is about 3.8 mm., and of the half-value layer about 0.3 mm. Thus its maximum effect is confined to the bladder epithelium, leaving the sub-epithelial tissue almost unirradiated. Its colloidal nature protects against its resorption.

This preliminary report is based on our experience with radioactive colloidal gold (^{198}Au) in the treatment of superficial malignant lesions of the bladder since May, 1955. Our material included papillary cancer and also recurring extensive papillomata without histological cancer. Three cases are here briefly reported.

Methods

The radioactive material was obtained from Harwell. After the decision to use the colloidal gold method, fluid intake was restricted on the day prior to treatment and forbidden on the day of treatment. When the activity in millicuries per millilitre had been determined, the desired dose in millicuries was drawn into the lead-shielded syringe and introduced into the bladder through an ordinary bladder catheter. Injection was readily accomplished after removal of urine by catheter. Sterile isotonic saline solution was used for rinses. At an appropriate time the contents of the bladder were run off, and the bladder was washed out with a warm solution. The volume of the removed fluid was measured for dose calculation. With suitable precautions the personnel received no hazardous amounts of radiation.

Most patients received approximately 300 mc. of gold. The range was 100 to 375 mc., the former amount being used in one instance because no more was available at the time. The injected gold was retained in the bladder for four to six hours. With the dose-rate formula of Walinder (1955) it was calculated that some 300 mc. should be given in about 70 ml. of saline; so that, taking into account the increase of volume of the bladder due to the flow of urine from the ureters, the total dose of beta- and gamma-radiation received by the bladder epithelium in six hours would be 4,000 to 5,000 r.

Case Reports

Case 1.—A 56-year-old man was seen for the first time in March, 1952, complaining of haematuria of one month's duration. Cystographic and cystoscopic examinations revealed a tumour about 4 cm. in diameter situated in the left of the bladder. The growth was removed by suprapubic electroresection and histologically reported as transitional-cell papilloma. During the following three years papillary tumours reappeared in the bladder serially, requiring six transurethral fulgurations and two suprapubic coagulations. The histological diagnosis was benign papilloma. As the repeated call for fulguration was thought to indicate a malignant change, it was decided to try radioactive colloidal gold radiation for multiple villous papillomata. On May 5, 1955, 300 mc. of gold was instilled into the bladder for six hours. Thus the bladder epithelium was estimated to have received a total dose of 4,640 r of beta- and gamma-radiation. Three weeks after instillation cystoscopic studies revealed a slight redness of the bladder mucosa. The tumour seemed to be eradicated. However, six months later cystoscopy revealed recurrent papillomata in the base of the bladder. Another treatment with radiogold was suggested, and on November 11, 1955, 215 mc. of radioactive colloidal gold was instilled into the bladder for six hours and twenty minutes. The estimated dose at the bladder epithelium was 3,860 r. When examined three weeks after instillation no tumour was seen in the base of the bladder. Four months after the second instillation, in March, 1956, cystoscopy revealed a small recurrent papilloma in the fundus of the bladder.

Case 2.—A 50-year-old man was referred in August, 1955, from another hospital with a diagnosis of tumour of the urinary bladder. Cystoscopic examination revealed a band-form area of low papilliferous tumour extending from the right ureteric orifice to the mid-portion of the right bladder wall. The biopsy specimen was reported as malignant papilloma. On August 11 100 mc. of radioactive colloidal gold was instilled into the bladder for six hours. The estimated dose at the bladder mucosa was 1,700 r. Ten days later an attempt at cystoscopy resulted in a marked haemorrhage presumably due to irradiation epithelitis. One month after treatment cystoscopic examination revealed a normal bladder except for an epithelial defect at the site where the tumour had been. Cystoscopy on September 26 showed the site of the tumour to be indistinguishable from the remainder of the bladder mucosa, but near the prostatic orifice there was a small polypoid tumour; this was removed by diathermy. The histological diagnosis of the tumour was polyp. On October 29, two and a half months after the radioactive gold treatment, there was no sign cystoscopically of any neoplastic lesion. The patient had no clinical evidence of tumour at the time of writing.

Case 3.—A 58-year-old man was admitted in May, 1955, with a history of haematuria of one month's duration. Cystoscopy revealed a papillomatous growth about 3 cm. in diameter lateral to the right ureteral orifice. The bladder was opened suprapubically, and the tumour was electroresected. The histological diagnosis was transitional-cell papilloma. In February, 1956, cystoscopy revealed multiple papillomata of various sizes at the operation scar. Furthermore, there were small villous dots throughout the bladder epithelium. The bladder was opened suprapubically and the scar was widely excised. Because of the multiplicity of growth it was decided to treat the patient with radioactive gold instillation. One month post-operatively, on March 14, 200 mc. of

radioactive gold solution was instilled into the urinary bladder for six hours. The estimated surface dose was 3,400 r. One month after instillation, cystoscopy revealed that the small multiple papillomata had entirely disappeared. In the fundus of the bladder there was a solitary persistent papilloma which was fulgurated transurethrally.

Discussion

It is our opinion that radioactive gold therapy yields good results in certain selected cases of bladder tumours. Each case, however, should be considered individually before deciding whether or not radiogold instillation is advisable. Primarily we divided our material into two groups, one including all papillary tumours and the other including non-papillary infiltrating solid carcinomas.

The essential character of the papillary type of cancer is that the lesion is superficial, involving only the mucosa of the bladder. The papillary type includes those formerly benign papillomata which have undergone malignant changes. However, it is difficult to say when the malignant change has developed. Small biopsy specimens can completely miss malignant portions of a papillary tumour and show only the innocent appearance of benign villous epithelium. Multiplicity is regarded by most urologists as an indication of malignancy. Our material included papillary cancer and recurring extensive papillomata without histological cancer.

Papillary tumours are well known to have a tendency to serial reappearances. Most of the patients received surgical treatment before the radioactive gold therapy, consisting of multiple transurethral or suprapubic fulgurations and segmental resection of the bladder. In some of the cases radioactive cobalt needles had been implanted. None of these patients received external x-ray treatment to the bladder.

Before instituting radiogold therapy we considered the histopathology, size, number, and location of the tumours of each case, as well as other complicating factors such as severe infection, with or without the formation of incrustations or stones, and severe haemorrhage. It is clear that infiltrating lesions cannot be treated by intracavitary instillation of radioactive gold because the dose received at depth will be too small to be effective. This method is designed to treat non-infiltrating lesions in which the tumorous lining is not beyond the range of the maximum penetration of the beta-rays emitted by radioactive gold.

We avoided instillation when thick papillomata were present in cases of multiple or extensive lesions. Nevertheless, when the small tumour seedlings and the thin frosting of tumour of the bladder epithelium have disappeared, small residual tumours might be easily eradicated by fulguration. In some cases bulky tumours were removed prior to instillation, leaving small villous tumours to be exposed to subsequent radioactive gold radiation.

The radiation dose in most cases ranged between 4,000 and 5,000 r, estimated at the mucosal surface. The doses were given as single exposures for four to six hours. In reference to dosage, Case 2 deserves special mention. Prior to the use of radioactive gold the patient had had no other treatment. Following intravesical instillation of 100 mc. of radioactive gold for six hours, the tumour had completely disappeared on cystoscopic examination. The estimated surface dose was 1,700 r. One patient (Case 3) had a persistent lesion following a dose of 3,400 r. It was borne out, in these cases, that villous tumours responded satisfactorily to adequate doses of intracavitary radioactive gold irradiation. Thick papillomata do not respond to the treatment.

In Case 1 new lesions developed in the bladder after radioactive gold therapy. This patient received two treatments of 4,600 r and 3,800 r, respectively. We do not expect, however, that even with higher doses all lesions will be permanently eradicated. Papillomatosis is a disease of the entire bladder epithelium, and radiation treatment will not, of course, prevent the development of new lesions.

In patients of this group, no significant bladder symptoms developed following treatment by radiation. Cystoscopically, the immediate reaction after radiogold instillation was

transient epithelitis, which subsided within the next weeks. No evidence of more severe tissue reaction was observed. None of the patients treated experienced radiation sickness characterized by the symptoms of lassitude, anorexia, nausea, or vomiting.

We know that the number of patients studied is not large enough or the time of observation long enough for conclusive evaluation of this method of treatment. However, we feel that the results to date are encouraging. Complete regression of the tumour was accomplished in cases of really superficial lesions. It is realized that any anatomical classification based on cystoscopic findings is subject to error. None the less, we believe that when the clinical findings are favourable this therapy should be considered as a primary measure.

Summary

Intracavitary instillation of colloidal radioactive gold (^{198}Au) was used for treatment of patients with multiple papillomata of the bladder. Approximately 300 mc. of gold was instilled into the bladder for four to six hours to deliver a dose of about 4,000 to 5,000 r to the bladder epithelium. The treatment had no harmful side-effects locally or on the general condition of the patient.

Three selected cases suitable for radioactive gold therapy are briefly reported.

It is our impression that this method is an excellent type of irradiation for really superficial malignant lesions. The method was used for treatment of multiple papillomatosis of the bladder alone or in conjunction with surgery.

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DIPIPANONE HYDROCHLORIDE AS AN ADJUNCT TO ANAESTHESIA IN OBSTETRICS AND SURGERY

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Balanced anaesthesia developed over recent years has been made possible by the introduction of a large range of drugs with specific actions. In 1947 Neff, of San Francisco, introduced pethidine into anaesthetic practice as an adjunct to nitrous oxide anaesthesia. Since then pethidine has proved itself as useful in the operating theatre as in the general and obstetric wards. Over the past 18 months we have investigated the use of another analgesic, dipipanone hydrochloride, in obstetrics and as an adjunct to general anaesthesia. This paper describes our results.

Pharmacology

Dipipanone hydrochloride (DL-6-piperidino-4,4-diphenylheptan-3-one), which is the piperidino analogue of meth-

adone ("physeptone"), was first described by Ofner, Thorp, and Walton in 1949. Its analgesic properties in animals were investigated by Ofner, Walton, Green, and White (1950) and by Green and Young (1951). Its use as an analgesic for the control of post-operative pain and that arising from a variety of acute and chronic medical conditions has been

Dipipanone hydrochloride

Methadone

reported on by Gillhespy, Cope, and Jones (1956). In man 25 mg. of dipipanone administered intramuscularly or subcutaneously is equi-analgesic with 10 mg. of morphine, 100 mg. of pethidine, or 10 mg. of methadone. The analgesic effect develops within 15 minutes and lasts from five to six hours. Nausea and vomiting are rare and there is no significant change in the blood pressure or pulse rate. As with morphine, the respiratory minute-volume is reduced mainly by a reduction in the respiratory rate; this effect, however, is less than that of an equi-analgesic dose of morphine. There is no appreciable hypnotic effect, and prolonged administration produces no significant change in the blood picture.

Dipipanone hydrochloride, like methadone, is metabolized in the liver and excreted in the faeces and urine. Therefore it should be used with caution in patients with severe liver or kidney disease.

Methods

Clinical Material.—The cases investigated were (1) a series of 53 consecutive obstetric cases which received dipipanone to relieve pain in labour (as a control pethidine was used in a further series of 53 consecutive cases); (2) a series of 200 general surgical cases which received dipipanone as an adjunct to general anaesthesia, and (3) a series of 100 thoracic surgical cases in which dipipanone was the main supplement to nitrous oxide anaesthesia and was used in place of a muscle relaxant.

Obstetric Cases.—During a period of one month, 53 consecutive patients were given dipipanone hydrochloride for the relief of pain in labour. As a control, a similar number of cases were treated with pethidine. For ease of statistical analysis, the midwife present at each delivery recorded the particulars of the case, the dose of analgesic given, the relief obtained, and the progress of labour on a specially designed form. The similarity of the two series of cases with respect to age and body weight will be seen from Table I.

General Surgical Cases.—Anaesthesia for the general surgical cases followed a standard technique. The patients were premedicated with papaveretum ("omnupon"), $\frac{1}{2}$ gr. (20 mg.), and hyoscine, 1/150 gr. (0.43 mg.), or with

TABLE I.—Age and Weight of Obstetric Patients

Age in Years:	15–	20–	25–	30–	35–	40–45	Total	
Dipipanone	3	20	17	11		2	53	
Pethidine	5	26	15	4	1	2	53	
Weight in Stones:	8–	9–	10–	11–	12–	13–	14–	Total
Dipipanone	7	12	14	9	7	1	3	53
Pethidine	10	9	19	10	3	2		53