Although the mortality in tetanus is higher in patients who have a pyrexia, this is not a constant feature in those dying from the disease. Pyrexia is probably due in every case to some degree of chest infection. The only constant feature in those dying from tetanus appears to be the presence of reflex spasms, which continue until death.

In our present state of knowledge the greatest hope of reducing the mortality from tetanus in Nigeria lies in prevention. While it is important to instruct the public how to avoid infection, the most rapid and most certain method of prophylaxis is by immunization with tetanus toxoid (Hampton, 1954; Emmett and Breck, 1955). A primary immunizing course of two injections of toxoid at an interval of six weeks, followed by a booster dose, will confer a lifelong immunity in most cases (Peterson *et al.*, 1955; Moss *et al.*, 1955). Production of tetanus toxin from a contaminated wound will further increase the immunity (Peterson *et al.*, 1955). To immunize the whole population of Nigeria against tetanus is a formidable task, but this must be the aim. The following is a suggested approach to the problem. (1) All schoolchildren be given a primary immunizing course of tetanus toxoid and at least one booster dose during their school years. As schooling has recently become compulsory, this would prove a comprehensive measure. (2) All expectant mothers be given a primary immunizing course of tetanus toxoid during pregnancy followed by a booster dose at parturition. (As a corollary to this it is suggested that all newborn children be given a protective dose of antiserum at birth.) (3) The remainder of the population be offered immunization as soon as the above groups have been dealt with. This approach is aimed at reducing the incidence of tetanus and is at present the most promising means of reducing the mortality.

Summary

A review is made of 100 consecutive adult cases of tetanus treated at University College Hospital, Ibadan.

The problem that tetanus presents in Nigeria is discussed with reference to incidence and causative injuries.

The importance is shown of assessing prognosis before deciding the method of treatment to be used and in estimating the value of different types of treatment.

The methods of treatment used, and their suitability for an area where the incidence is high, are described.

The value of antitetanic serum in the treatment of established tetanus is questioned.

Reduction of the incidence of the disease by prophylactic immunization is suggested as the most effective means of reducing the mortality.

I am indebted to Professor A. Brown and Dr. J. R. Lauckner for allowing me to treat and investigate these cases and for their advice and encouragement. I also thank all members of the medical and nursing staff of University College Hospital, Ibadan, who assisted in the care of these cases.

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MANAGEMENT OF SEVERE TETANUS

USE OF CHLORPROMAZINE IN TWO PATIENTS

BY

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Many drugs and techniques have been employed in the search for a safe and effective method of controlling the convulsions of severe tetanus. The ideal agent should abolish spasms and provide adequate sedation without respiratory depression. Chloral hydrate, bromides, paraldehyde, magnesium sulphate, morphine, pethidine, bromethol, and various barbiturates have been used, but all have defects. More recently muscular relaxant drugs have been employed with or without anaesthetic agents and artificial respiration. While their use is logical, the full regime involves many hazards and has not been shown to lower the mortality. Some of the most convincing recent series (Forbes and Auld, 1955; Veronesi, 1956) have been managed by more conservative methods.

Following reports of the experimental and clinical control of the muscular spasms of tetanus with chlorpromazine, we determined to explore its possibilities as the mainstay of sedative and anticonvulsant therapy. This drug has been shown experimentally to have properties which make it likely to be of value in tetanus. It antagonizes some central convulsant drugs (Courvoisier *et al.*, 1953); in cats it inhibits motor activity induced by cortical stimulation and suppresses the postural responses which occur on stimulation of the cerebellar cortex and the reticular formation (Dasgupta and Werner, 1955); it abolishes local tetanus in rabbits (Hougs and Andersen, 1954; Kelly and Laurence, 1956). The injection of chlorpromazine in cats has been shown to prolong the action of relaxant drugs such as *d*-tubocurarine and mephenesin (Courvoisier *et al.*, 1953); further, it has a direct paralytic effect on skeletal muscle (Burn, 1954).

These qualities, together with its better-known central effects as a tranquillizing agent and sedative and in potentiating the effect of hypnotic and analgesic drugs, suggest that its use in tetanus is rational. There are relatively few clinical reports of its use in the disease. Most of those that have appeared describe it as a useful adjunct in therapy (Adriani and Kerr, 1955; Bodman *et al.*, 1955) or discuss its use in mild and moderate cases (Cole and Robertson, 1955). Others have considered it a failure (Andersen *et al.*, 1955). In all these instances the doses used were small.

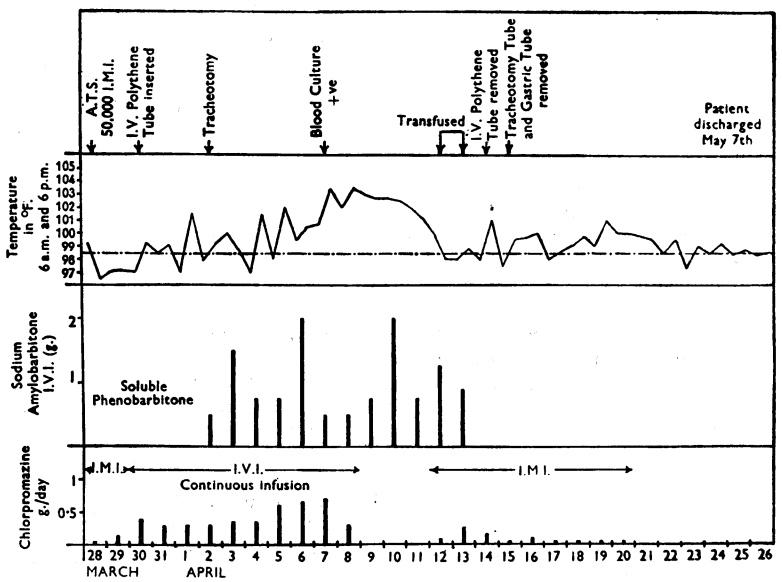
Our approach to the problem has been more in line with that of Kelly and Laurence (1956). We had previously observed the effect of chlorpromazine in four patients with mild tetanus in whom it relieved muscular

rigidity and minor spasms. It is the purpose of this paper to describe the use of the drug in two children with severe tetanus and to draw certain conclusions from this experience.

Case 1

The patient, a boy aged 14, was admitted to this hospital complaining of jaw stiffness and tightness in the chest for one day. Fifteen days earlier he had sustained a splinter wound to his right ankle. Six days before admission he had been given tetanus antitoxin and penicillin; the dose of both was uncertain. On admission he appeared anxious, trismus was evident, and there was slight rigidity of the upper abdominal muscles. Blood pressure was 135/80, pulse rate 80, and temperature 98° F. (36.7° C.). Mild tetanus was diagnosed. He was confined to bed, given a further 50.000 units of antitoxin intramuscularly, and 500,000 units of penicillin eight-hourly. Debridement of his wound was not performed. He was sedated with chlorpromazine, 50 mg. intramuscularly every six hours, combined with soluble phenobarbitone, 3 gr. (0.2 g.), intramuscularly three or four times daily as required. His symptoms were at first well controlled in this way, but within 48 hours of admission several severe spasms occurred with marked opisthotonos, a rigid abdomen, and increase in extensor tone of the lower limbs. The respiratory excursion was reduced, but laryngeal spasm and cyanosis did not occur.

By the third day feeding by mouth was impossible, so a "polythene" catheter was introduced into the right long saphenous vein and advanced into the inferior vena cava. For the next fortnight all nutrition and drugs were administered by this route, and for three days soluble phenobarbitone, 1½ to 3 gr. (0.1 to 0.2 g.), and chlorpromazine, 50 mg., were injected intermittently into the infusion set. Control of rigidity and spasms was effective for a time, but it became clear that the effect of the drugs in these doses was transient and inadequate.



Case 1. Temperature chart and record of treatment with amylobarbitone and chlorpromazine.

On the sixth day after admission the patient had three major spasms with respiratory embarrassment, stridor, and some cyanosis. It was then obvious that he had severe tetanus and that a more vigorous plan of treatment was necessary.

Tracheotomy was performed and a continuous intravenous infusion of chlorpromazine with supplements of sodium amylobarbitone administered. No subsequent major spasms occurred, although we observed a number of minor ones. Generally he lay with hypotonic limbs and ptosed eyelids, although varying degrees of neck and spinal rigidity and rigidity of his abdominal muscles persisted. Breathing was not depressed except when too much amylobarbitone was given; it was deep and effective, and his colour remained good.

Following tracheotomy the patient was under constant medical and nursing supervision. Careful attention was paid to nursing procedures. Every two hours he was turned, and oral, nasal, and skin hygiene and tracheotomy toilet were carried out, tracheo-bronchial secretions were carefully removed by controlled tracheal suction, and postural drainage was employed; no major pulmonary complications occurred. It was possible to maintain him in good fluid and electrolyte balance by the administration each day of 2–3 litres of fluid, containing 10% glucose and 10% alcohol, in either 0.9% saline or distilled water with daily supplements of 70–80 mEq of potassium (as 1.08% potassium chloride), 25 g. of serum albumin, and vitamins B, C, and K. His intake of about 2,200 calories daily was adequate. Full intravenous feeding was continued until he could swallow satisfactorily. A blood transfusion of 2 units of packed red cells was given on the 16th day because of an anaemia of 10 g. per 100 ml.

A blood culture taken on the 11th day, after nine days of intravenous therapy when the temperature had reached 103° F. (39.4° C.), grew *Staphylococcus pyogenes*, which was insensitive to penicillin, streptomycin, chlortetracycline, oxytetracycline, and chloramphenicol. It was sensitive only to erythromycin and novobiocin. Erythromycin was therefore given intravenously in a dose of 4 g. daily from the 11th day for one week, and thereafter by mouth. From the 13th day, 2 g. of novobiocin was given daily by intragastric tube, and later orally. These drugs were supplemented on the 15th day with intravenous penicillin, 100 million units daily, and subsequently intramuscular doses of 12–18 million units daily with 0.5 g. of probenecid. This severe septicaemia was ultimately controlled without evidence of abscess formation. There were no signs of endocarditis. Antibiotics were gradually reduced and finally stopped on the 35th day in hospital. Lumbar puncture and electroencephalogram during the patient's last week in hospital were normal.

Chlorpromazine by continuous infusion and sodium amylobarbitone given as a supplement intermittently into the infusion apparatus were the sole sedative agents. The dosage and period of administration of each may be seen in the Chart. It was interesting that in the fulminating phase of the septicaemia the boy's sedative requirements fell considerably. For three days there appeared to be no manifestations of tetanus. However, as the septicaemia was controlled, rigidity and minor spasms recurred and further intramuscular chlorpromazine was required. On the 24th day, when the drug was withdrawn, all deep reflexes were increased and bilateral knee and ankle clonus were present. Spasticity and hyperreflexia in the muscles of the right leg and ankle—the region of the original wound—were especially marked. These gradually subsided by the 34th day. At this time the patient had been afebrile for five days; he was walking satisfactorily and eating well, with no trismus. There were no subsequent complications, and he was discharged 41 days after admission.

Comments.—Certain points in the administration and effect of these drugs are worth recording.—(1) Chlorpromazine was effective in relieving major spasms, although modified minor spasms were frequently observed, especially if the trachea were aspirated roughly. The patient could be catheterized without provoking a spasm. (2) Sodium amylobarbitone was necessary, but the amounts required

were small. (3) So long as the amount of amylobarbitone administered was small, there was no sign of respiratory depression, and the state of consciousness was never deep. (4) When attempts were made to reduce the dose of chlorpromazine three days after it had been started, spasms recurred. (5) Chlorpromazine diminished tracheo-bronchial secretions. (6) The drug caused no complications other than a depression and irritability which persisted for some two weeks after its cessation. There was no jaundice, and liver function tests remained normal.

Case 2

On April 7, 1957, a girl aged 12 was admitted to Tamworth Hospital, New South Wales, because she had complained of a stiff neck for four days. For three nights she had bitten her tongue in her sleep and she was unable to open her mouth. After two definite spasms the diagnosis of tetanus was made. There was no history or sign of recent injury; a possible source of infection was a dental local analgesic given four weeks previously. She was given 200,000 units of tetanus antitoxin intravenously and 100,000 units by intramuscular injection. Penicillin, 1 million units six-hourly, and streptomycin, 0.5 g. twice daily, were given.

By April 10 spasms were so severe and numerous as to cause serious respiratory embarrassment. A tracheotomy was therefore performed. Up to this point relief of spasms had been achieved with intravenous sodium thiopentone, together with pethidine, a little chlorpromazine, and soluble phenobarbitone.

The patient was transferred 280 miles by ambulance to this hospital, where she was admitted on April 11. In transit, during a severe spasm, the tracheotomy tube was ejected. On admission she was barely responsive to painful stimuli, and was rigid and cyanosed. Respiratory movements were of shallow amplitude and the respiratory rate was 28 a minute; the pulse rate was 150, and body temperature 100.2° F. (37.9° C.). She was removed to the operating theatre, where the tracheotomy tube was reinserted and an intravenous infusion begun through a polythene catheter into the right cephalic vein. For these procedures sodium thiopentone, sodium amylobarbitone, chlorpromazine, and a little succinylcholine were given. She was returned to her bed about 10 a.m., and during the next six hours received a further 0.5 g. of amylobarbitone to control two generalized spasms. Her respirations were shallow and depressed, and she became cyanosed. The untoward effect of a combination of many drugs in large doses over 24 hours was obvious. Amylobarbitone was stopped, and at 5 p.m. the administration of intravenous chlorpromazine was begun. Within two hours, after 100 mg. had been given, breathing was deeper and her colour more satisfactory; muscular relaxation was more adequate, and there was no further sign of a generalized convulsion.

From this time the patient was constantly attended by a member of the resident medical staff. Only those whose nasal swabbings were free from staphylococci were permitted to enter her room, and all wore sterile gowns and gauze masks while in attendance. Before handling any of the intravenous apparatus the medical officer scrubbed his hands in germicidal soap and donned a sterile theatre gown and sterile rubber gloves. Every two hours the patient was turned to alternate sides and pressure areas were attended to. The trachea and bronchi were aspirated regularly and a self-retaining indwelling urethral catheter was inserted.

Nutrition and drug therapy were given intravenously. The patient received each day approximately 2 litres of fluid containing 10% glucose and 10% alcohol in either 0.9% saline or distilled water, 1.08% potassium chloride, antibiotics, vitamins B and C, and 25 g. of serum albumin. No sedative or relaxant drugs other than chlorpromazine and sodium amylobarbitone were used. The former was given as a constant infusion and amylobarbitone in a 2% solution as a side drip as required.

Progress

On the day of admission *x*-ray examination confirmed the diagnosis of pneumonia in the left lower and mid-zones. Postural and percussion drainage was carried out for two weeks. "Alevaire" dispersed in carbogen was administered for 5–10 minutes hourly. By the following day the pneumonia had advanced clinically and radiologically, and the body temperature reached 102° F. (38.9° C.). Oxytetracycline, 2 g. a day intravenously, was substituted for penicillin and streptomycin. Bronchoscopy permitted the aspiration of several plugs of yellow mucopus.

By the third day in hospital very little muscular rigidity remained, and there had been no spasm since the start of the chlorpromazine infusion. Some lightening of consciousness occurred over the next 48 hours despite unchanged doses of chlorpromazine; the patient would stir in response to painful stimuli. Five days after admission all sedation was withheld for a trial period, and within three hours marked muscular rigidity and opisthotonos were obvious, although no frank spasms occurred. The injection of 50 mg. of chlorpromazine rapidly brought about a reduction of muscle tone.

On the sixth night larger doses of chlorpromazine were required and the 24-hour total reached 950 mg. The girl was restless and upset at this time, and in retrospect it appeared that a little amylobarbitone would have been more effective. Next day, the seventh since admission, a partial pulmonary collapse gave rise to laboured respiration with a sudden rise in temperature and pulse rate. Aspiration of a large lump of mucopus from the left bronchus relieved the condition. By now the girl's state of consciousness was such that she muttered coherent phrases, although she showed no tendency to spasm. This was a vivid contrast with her state on admission, when, despite barbiturate sedation to the point of respiratory depression, she was still rigid and subject to spasms.

On the eighth day slight cyanosis and distressed respiration marked a further exacerbation of atelectasis and bronchopneumonia. This improved over the next 48 hours, during which time copious secretions were aspirated from the trachea and bronchi. At this time she was transfused with 2 pints (1,140 ml.) of whole blood because her haemoglobin value had fallen to 10.1 g. per 100 ml.

By the 13th day her general condition was improved and her mental state such that she understood simple commands. Infusion of chlorpromazine, sodium amylobarbitone, and alcohol ceased at 2 p.m. Five hours later she held a short conversation with her attendants. Next morning she took fluids by mouth and breathed freely after the tracheotomy was blocked. The tube was later removed and intravenous therapy discontinued. Tetracycline, 100 mg. eight-hourly intramuscularly, was continued until 17 days after admission.

For six days after cessation of chlorpromazine she remained apathetic and took little interest in her surroundings. Her features were immobile, she spoke in monosyllables, as though with effort, and usually had to be fed. This state cleared rapidly on the seventh day and she became mentally normal. It was undoubtedly a Parkinsonian reaction such as has been described after heavy dosage with chlorpromazine. Apart from this, and a mild jaundice, she continued to improve and was fit to go home on May 11.

Successive daily doses of chlorpromazine (C.) and sodium amylobarbitone (S.A.) in mg. were:

Day:	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C.	200	500	450	350	350	950	650	625	550	450	225	150	50	0
S.A.	500	500	0	300	125	100	500	0	300	0	300	200	100	0

Comments.—The effects of chlorpromazine and sodium amylobarbitone in combination, noticed in this case, were essentially the same as in Case 1. However, mild

jaundice with a serum bilirubin level up to 3 mg. per 100 ml. developed on the 13th day of chlorpromazine therapy. This subsided quickly, and liver-function tests were normal on discharge from hospital. Bronchopneumonia was established on arrival at this hospital. This and atelectasis were the chief hazards of the illness. They were adequately controlled with antibiotics, physiotherapy, postural drainage, bronchoscopy, and regular suction of trachea and bronchi. The irritant solutions which were given through the polythene catheters caused a severe thrombophlebitis in each vein into which polythene was inserted. Peripheral veins were used in the hope of lessening the chances of septicaemia. In each case swelling and erythema subsided after four or five days.

Discussion

Both these children suffered from severe tetanus with generalized convulsions which were increasing in frequency and severity at the time when intravenous chlorpromazine was begun. In neither instance was the disease of the fulminating, rapidly progressive type which seems to make all therapeutic efforts futile. In both children respiratory embarrassment and cyanosis had become a feature of the spasms. In Case 1 the use of suxamethonium, with intermittent positive-pressure respiration, was planned, but it was rendered unnecessary by the success of the chlorpromazine–amylobarbitone regime. This led to use of the latter in the second patient, who would also probably have been managed with relaxants and artificial respiration.

Sedation

The relative ease with which the muscular spasms of these two patients could be controlled was gratifying. The combination of chlorpromazine with small quantities of sodium amylobarbitone was both simpler and more satisfactory than any drug or combination of drugs used previously in this hospital in the management of tetanus. The adequate control of violent spasms without deep anaesthesia or respiratory depression was in striking and strong contrast to the effects of drugs such as rectal bromethol or sodium thiopentone by intravenous infusion.

Previous reports have with one exception (Kelly and Laurence, 1956) described the use of, at most, moderate doses of chlorpromazine. Amounts of up to 200 mg. daily have been given. Our plan was to increase the dose so long as the drug's effect continued and there were no signs of serious sensitivity or toxicity. Accordingly these children received, for nearly two weeks, a constant infusion of chlorpromazine in amounts varying mostly between 400 and 600 mg. daily. Supplementary injections of 50 mg. were given as were required. In neither child did a major spasm occur after the drug was begun. Muscular rigidity was lessened but not abolished. In both children, but particularly in Case 1, some neck and abdominal rigidity was often present. The limbs were generally hypotonic and ptosis was evident. When the patient became rigid or a minor spasm occurred the injection of 50 mg. of chlorpromazine was rapidly effective in relieving it. There were many occasions when the children became restless, with jerky irregular breathing that was neither shallow nor depressed. These periods seldom lasted for more than a few minutes, and they appeared to be the equivalent of major spasms with the violent motor component removed. The level of consciousness was seldom deep, except when too much amylobarbitone was given in a single injection or when it was repeated too soon. These were also the only occasions when respiration was shallow and inadequate.

Tolerance to the hypnotic effects of chlorpromazine occurred in both patients. This is a common experience in psychiatric patients who take large doses of the drug. Less tolerance developed to its relaxant properties; that some did so is suggested by the increase of approximately one-third in daily dosage in both patients by the end of the first week of infusion. How far this tolerance might develop with prolonged administration is not known, but it is probable that there is a maximum effective dose beyond which any increase is futile. This raises the problem of control of convulsions in the overwhelming, rapidly progressive case of tetanus, and the extent to which chlorpromazine might be effective. It is likely that further drugs would be required for adequate control.

When chlorpromazine is employed as a sedative or tranquillizing agent it is often desirable to administer another drug because of its effect in potentiating the action of other sedatives. Sodium amylobarbitone was chosen because experience had shown it to be effective, rapid, safe, and easy to control when given in small doses. To avoid respiratory or circulatory depression it is important to give small quantities of the drug frequently rather than large doses occasionally. In these children the daily amount varied between none and 2 g. Nearly always less than 1 g. was given, and rarely was a dose of more than 200 mg. required at a time.

It was found that the balance in dosage between the two drugs was at times delicate. It was easy to give too much of one or the other. In Case 2 on one day 950 mg. of chlorpromazine was given—400 mg. during a few hours when she was particularly restless. It was without effect; but the addition of 300 mg. of amylobarbitone produced peaceful sleep, and it was clearly the drug required.

We were unable to detect any gross signs of tachycardia or fall in blood pressure or temperature attributable to chlorpromazine. No doubt they occurred to some extent, but there were no indications to suggest that such large intravenous doses should not be used. There were no signs of skin sensitivity or bone-marrow depression. In Case 2 mild jaundice developed toward the end of the second week of chlorpromazine administration, but this was transient and resolved quickly. This girl also had Parkinsonian symptoms for a week after withdrawal of the drug, and at the same time both children were in an abnormal mental state characterized by varying degrees of apathy, irritability, and depression.

Other Aspects of Management

This is no place for a full discussion of the treatment of tetanus, but some points deserve reference. During the severe phase of their illnesses these children were constantly attended by a member of the resident medical staff, which was organized into a team for this purpose. We regard this as a necessity in severe tetanus because there is no other reliable method of meeting the many sudden hazards which may occur.

While acutely ill and unable to swallow, both patients were fed entirely by vein. In the past five years nine patients with severe tetanus have died in this hospital, and at least three of these deaths were precipitated by the inhalation of gastric contents in patients fed by intragastric tube. So, apart from its effect in provoking spasms, we are averse to intragastric feeding.

Previously healthy individuals in a good state of nutrition can be adequately maintained with intravenous fluids during the critical week or fortnight of an exhausting disease like tetanus. It was possible to keep these children in satisfactory fluid and electrolyte balance for this period. The use of either 0.9% sodium chloride, or distilled water, containing 10% glucose and 10% alcohol, provided a tolerable intake of approximately 2,000 calories a day. The alcohol might have helped in sedation.

In Case 1 an almost fatal septicaemia occurred which was caused by a *Staph. pyogenes* resistant to all antibiotics in common use. Only erythromycin and novobiocin in large doses were effective in controlling it. There seems no doubt that this septicaemia originated from the polythene tube in the inferior vena cava. It resulted in a far more careful technique in all dealings with the intravenous apparatus in Case 2.

A further problem lies in the technical difficulty of infusing powerful and irritant solutions over a long period. Nevertheless, we feel that the advantages of full intravenous alimentation outweigh any shortcomings.

Summary

Two severe cases of tetanus in children are described. Large doses of chlorpromazine controlled the convulsions satisfactorily. The drug was given by a continuous intravenous infusion and was supplemented by small quantities of sodium amylobarbitone. Further relaxant or sedative agents were unnecessary. There were no serious toxic or sensitivity effects caused by chlorpromazine. Certain other points in the management of severe tetanus are discussed.

We thank Dr. A. W. Morrow and Dr. K. S. Harrison, honorary physicians in charge of these patients, for their guidance and for permission to publish this paper. We thank our colleagues on the resident medical staff and the nursing staff of the Royal Prince Alfred Hospital, in particular Sister W. Sanderson and Sister E. Parry Evans, for their care and help.

ADDENDUM.—Since this paper was submitted for publication, five patients suffering from tetanus have been admitted to this hospital. In three the disease was severe. These patients were managed according to the same plan with chlorpromazine and a barbiturate. This experience has helped to confirm the views expressed in the paper. All the patients have recovered, and we have observed no serious untoward effects from the intravenous administration of large quantities of chlorpromazine.

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A SIMPLE CYTOLOGICAL TEST FOR CANCER CURE

BY

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In the course of routine screening of vaginal smears carried out at the Cytological Laboratories of the Hammersmith Hospital during the past seven years our attention was aroused by the frequent association of malignant growth in the genital tract with highly oestrogenized smears.

Estimation of oestrogens by cytology can be done in two ways: (1) by evaluation of smear patterns—that is, taking the prevailing cell type into consideration (smears with a high oestrogenic inference show a predominance of superficial squamous cells, whereas atrophic smears are mainly composed of basal cells); and (2) by estimation of the cornification index (C.I.) (de Allende and Orias, 1950; Wachtel and Plester, 1954). The latter method, as employed by us, implies a count of 200 consecutive superficial and intermediate squamous cells and determination of the percentage of cornified cells—that is, those with pyknotic nuclei. We deliberately exclude the basal cells from this count, since they are invariably increased in the presence of infection owing to superficial erosion of the mucosa by the infecting organisms and exposure of the deeper basal layer, from which exfoliation then occurs. Cancerous growth in the genital tract is often associated with infection, and the presence of large numbers of basal cells in such cases would be wrongly interpreted as evidence of atrophy. The figures of C.I. obtained in this way are reproducible by different observers and show little individual variation (observer error).

Results

With the above technique (Wachtel, 1956) it was found that, as a rule, normal post-menopausal women had cornification indices below 10, usually below 5, provided, of course, that no oestrogens had been administered. In cases of oestrogen medication—by mouth, injection, implant, or vaginal pessary—the normal post-menopausal smear pattern changed profoundly from an atrophic to a proliferative appearance, with a simultaneous sharp rise in C.I. This sequence, with the demonstrable sharp rise in C.I. after oestrogen administration, was taken as a strong indication that the C.I. was actually a kind of yardstick for oestrogen evaluation.

Most patients with cancer in the genital tract showed high C.I.s. This finding is meaningless in premenopausal women, since naturally there are cyclical as well as individual variations in C.I. in normal premenopausal women and it would be impossible to establish what "a normal C.I. reading" should be at a given day of the menstrual cycle. Comparison of the individual figures of C.I. at ovulation time—that is, peak values—of a random sample of gynaecological out-patients attending the Hammersmith Hospital showed that the readings varied between 10 and 55. The fact that the C.I.s in pre-menopausal patients with gynaecological cancers were found to be high, but within the range of 20–60, was therefore of no statistical significance. However, of our post-menopausal cancer patients, 90% showed raised C.I.s—that is, values over 10—and the frequency of this phenomenon was regarded as significant.

The source of this excess oestrogen is obscure. For various reasons we were not sufficiently satisfied to ascribe this finding to adrenal and/or pituitary activity. Therefore, as an alternative hypothetical explanation, the assumption was made that the tumour itself might be capable of oestrogen production. Accordingly it was assumed that if this were so the C.I. would revert to low values after removal or destruction of all viable tumour tissue, whereas it would remain high if treatment had failed.

Preliminary investigations on patients with known recurrent malignant disease and on patients regarded as "cured" seemed to confirm our hypothesis (Wachtel, 1956) and encouraged us to use the C.I. as an indicator of success or failure of treatment.

In the last two years smears were taken from 165 patients at each attendance at the Gynaecological Cancer Follow-up Clinic of the Hammersmith Hospital, and the C.I., as well as the presence or absence of malignant cells in their vaginal smears, was noted. These patients were aged 24 to 80 years and had received treatment for different malignant conditions—for example, carcinoma of the vulva, Paget's disease of the vulva, squamous carcinoma of the vagina, squamous carcinoma of the cervix (all stages), adenocarcinoma of the endocervix, endometrial carcinoma, adenocarcinoma of the ovaries, cystadenocarcinoma of the ovaries, adenocarcinoma of the colon with secondaries in the ovaries, etc. The length of the follow-up period varied greatly, some having received radical treatment as long as 10 years previously and some only a few months back. Most of them, however, had been under observation for between one and two years.

Of these 165 patients, 111 showed no evidence of any clinical, histological, or cytological recurrence and had C.I. readings of under 10; while 37 had C.I. readings of over 10 and other evidence of remaining disease was found later. Nearly all these recurrences were cytologically predicted—that is, the high C.I. was the first evidence of remaining disease; in only seven cases was clinical evidence of persisting malignant growth present at the time the cytological prognosis was made. Nine patients had C.I. readings of