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

over 10 and no clinical evidence of recurrence at the time of writing this paper, and remain under observation; in four of these cases the observation period—that is, the time elapsed since completion of radical treatment—has not yet exceeded six months. In eight patients there was clinical and histological evidence of recurrence without rise in C.I.

Discussion

If we omit the nine cases showing high C.I. readings and no evidence of persisting or recurring neoplastic disease, because the observation period is too short to be conclusive evidence of prognostic error, it appears that a correct cytological forecast based on C.I. readings had been made in 148 out of 156 cases (94.8%). In eight (5.2%) instances the cytological prognosis based on low C.I. values was proved wrong. The 37 cases in which a correct diagnosis of persisting malignant disease was made are summarized in the accompanying Table.

It was interesting to note that, in some of the patients in whom the C.I. had remained high after full radiation treatment and histological proof of the cytologically postulated failure to respond had been obtained, subsequent surgical treatment produced a sharp drop in cornification values. These patients are presumably cured. However, in other cases the C.I. failed to drop even after additional surgery, and it is assumed that in these patients malignant disease persists. The following case histories illustrate these points.

Case 19.—Stage I cancer of the cervix was treated by two radium applications and deep x-ray therapy; treatment was completed in November, 1956. C.I. readings at the first follow-up attendance in December showed a C.I. of 23. Biopsy confirmed persistence of malignant disease, and Wertheim's hysterectomy was carried out on January 2, 1957. Lymph-node in-

volvement was not detected. Subsequent C.I. estimations on three occasions were all below 10.

Case 29.—In January, 1956, cancer of the cervix was treated with full radiation doses. The C.I. was 17 in April, 27 in May, 35 in June, and 36 in July, when malignant cells also appeared in the smear. Wertheim's hysterectomy was carried out in August, and residual disease was found in the anterior lip of the cervix and lower part of the body. Post-operative C.I. estimations at monthly intervals varied between 18 and 31. A fairly hard, large mass was present in the pelvis, but it has not yet been established clinically whether this is due to fibrosis or to remaining disease.

Case 4.—Cystadenocarcinoma of both ovaries in 1949 was treated by supravaginal hysterectomy and bilateral salpingo-oophorectomy, followed by deep x-ray therapy. The C.I. started to rise in May, 1956, and was 32.5 in November. Subsequent biopsy of the endocervix revealed the presence of a small papillary adenocarcinoma with slight mucin secretion, the histology being identical with the lesion found in the ovaries in 1949. The patient was then treated by radiotherapy (two radium insertions). Subsequent C.I. estimations varied between 23 and 29.5. Repeat biopsies in April, 1957, showed evidence of residual tumour tissue.

Failure of Treatment Without Rise in C.I.

In eight cases secondary or residual growth was present without rise in C.I. Three of these patients were premenopausal before treatment had been given. Of the five post-menopausal women each had a low C.I. before treatment. As had been shown in our preliminary investigations, the great majority of malignant tumours, but not all, are associated with high C.I. values; it would therefore be illogical to expect high oestrogenic values after treatment in persisting disease, in the absence of high C.I.s before treatment. In order to increase the value of the test it would therefore be advisable to study pre-treatment C.I.s

Summary of 37 Cases in which Persisting Malignant Disease was Diagnosed

Case	Age	Type of Growth	Treatment	C.I. After Treatment	Result
1	63	Ca cx Stage II. Stump ca, April, 1954	DXRT	20, 7/6/55, 23, 11/10/55	Gland biopsy, March, 1956, positive, Death from ca
2	43	Ca cx Stage II, Jan., 1955	RT	28, 15/2/55	Glands in parametrium, Jan., 1956. General carcinomatosis, death
3	79	Ca ovarii, 1953	Ovariectomy, 1955. Post-op. DXRT	12, 28/2/57	Alive, but abdominal tumour present
4	50	CystadenoCa, ovarii, 1949	Subtotal hysterectomy, BSO, DXRT	32.5, 15/11/56	Recurrence in cervical stump, 27/11/56
5	66	AdenoCa colon, 1950. Ca cx Stage III, 1955	Resection, RT	12, 26/3/56	Residual growth confirmed by biopsy, 26/3/56
6		AdenoCa body and ovaries, 1950	Hysterectomy, RT	40, 8/11/56	Vault recurrence diagnosed, 1953. Slowly progressing
7	42	Ca cx Stage II, Sept., 1955	RT	14.5, 25/11/55	Clinical recurrence, March, 1956
8	52	Ca cx Stage II, Feb., 1956	RT	16, 13/5/56	Biopsy: failure to respond, July, 1956
9	51	Ca cx Stage II, Feb., 1956	RT	16, 5/4/56	Biopsy: failure to respond, 13/4/56
10	58	Ca colon, 1955	Colectomy	17, 29/3/56	D. and C. laparotomy. Recurrence in uterus and ovaries, Mary, 1956
11	71	Paget's disease of vulva	RT, 1944. Vulvectomy, 1948, 1953, 1955	10.5, 28/8/56	Extensive Paget's disease vulva and vagina, 31/8/56
12	69	CystadenoCa ovary, 1953	Pelvic clearance, RT	12, 18/10/56	Pelvic mass, 11/4/57
13	46	Ca cx Stage III, Sept., 1955	RT	14, 12/4/56	Hard mass in pelvis, 12/4/56. Death, 6/8/56
14	53	Ca cx Stage I, Oct., 1955	RT	14, 21/6/56	Biopsy: failure to respond, 21/6/56
15	50	Papillary adenoCa ovaries, Feb., 1956	Pelvic clearance, RT	12, 5/4/56	Gland secondaries, May, 1957
16	56	Ca cx Stage III, May, 1956	RT	28, 6/12/56	Spinal secondaries, 10/1/57. Death from general carcinomatosis
17	39	Ca in situ, 1953	Wertheim	55, 6/8/53	Recurrence in vagina, May, 1955
18	53	Ca cx Stage III, May, 1956	RT	18, 26/7/56	Recurrence in vagina, March, 1957
19	33	Ca cx Stage I, Oct., 1956	RT	23, 6/12/56	Biopsy: failure to respond, 19/12/56
20		Ca breast secondaries	RT	20, 13/3/57	Spinal secondaries
21	38	Ca cx stump, Sept., 1955	1 radium insertion, Spain 1955. Surgery England, stump and ovaries removed Aug., 1956	13.5, 4/10/56	Persisting ca
22	58	Endocervical Ca, 1955	3 x radium	35, 14/7/55	Failure to respond hysterectomy. Extensive adenoCa in utero, 14/10/55
23	43	Ca cx Stage I, 1953	Panhysterectomy	15, 16/7/54	Ca in situ vaginae, 20/7/54
24	80	Sarcoma ovaries, Nov., 1956	Ovariectomy, RT	14, 4/4/57	Hard masses in abdomen
25	48	Anaplastic Ca cx, June, 1955	Wertheim, RT	14.5, 27/1/56	Death from general carcinomatosis, 11/12/56
26	49	Ca cx Stage IV, July, 1955	Palliative, RT	19, 9/1/56	Glandular secondaries on E.U.A. exam., 9/1/56
27	48	Ca cx Stage III, Oct., 1955	RT	10.5, 9/2/56	Mass in pelvis, March, 1956. Death from general carcinomatosis, 8/10/56
28	40	Ca cx Stage III, May, 1956	RT	19, 11/10/56	Bone secondaries diagnosed, Nov., 1956
29	48	Ca cx Stage II, Jan., 1956	RT	17, 20/4/56	Biopsy: Aug., 1956, failure to respond
30	57	Endometrial Ca, July, 1956	Total hysterectomy, Aug., 1956	16, 2/11/56	Secondaries in vagina
31	58	Ca ovary, secondaries omentum, April, 1956	Palliative RT partial hysterectomy	18, 28/6/56	
32	65	AdenoCa body, Sept., 1955	Pre-op. radium, 8,000 mg./hours. Wertheim	26, 23/10/55	Secondaries in vagina, March, 1956
33	42	Ca cx Stage I, Aug., 1956	RT	23, 21/12/56	Biopsy: failure to respond, 21/2/57
34	44	AdenoCa EndoCx, April, 1956	Hysterectomy, RT	19, 28/6/56	Secondaries in vagina, 13/9/56
35	49	AdenoCa body + Cx 1951. Recurrence in utero, July, 1955	3 x radium, 1951 DXRT, 1955	18, 22/3/56	Widespread secondaries 31/12/56
36	80	Pseudomucinous cystadenoCa ovarii, March, 1956	Palliative, RT	14, 7/6/56	Persistent growth
37	66	Ca ovarii, July, 1955	Hysterectomy-BSO	13, 8/11/55	Death from general carcinomatosis, 17/12/56

Ca=Cancer. Cx=Cervix. DXRT=Deep x-ray therapy. RT=Radiotherapy. BSO=Bilateral salpingo-oophorectomy.

whenever feasible. Failing this, we regard high C.I. readings after completion of radical treatment (allowing a three-months period to elapse in the evaluation of pre-menopausal cancer patients after radiotherapy) as suggestive of persistence of neoplastic disease, provided, of course, that no oestrogens had been administered. A low C.I. reading during the observation period after completion of treatment is regarded as a favourable prognostic omen only in cases in which pre-treatment C.I.s had been high.

It is not yet established whether our original hypothesis, that malignant tissue is capable of oestrogen production, is correct. In a few of our own cases urinary oestrogen estimations have been undertaken, and we are greatly indebted to Dr. Ian Ferguson Sommerville for kindly carrying out these investigations at the Endocrine Laboratories of the Institute of Obstetrics and Gynaecology in the Chelsea Hospital for Women. In the few patients investigated urinary oestrogen excretion was high and compared well with the high C.I. readings. However, these data are as yet incomplete and no conclusions can be drawn from them, although other authors (Young *et al.*, 1957) showed similar good correlation on a larger material.

The frequency with which a high C.I. reading is associated with malignant disease in the female genital tract is significant enough to suggest the use of it as a test for cure.

Summary and Conclusions

C.I. estimations in patients who had received radical treatment for malignant disease in the genital tract seemed to be of great diagnostic help in the recognition of failure of response or in the detection of early recurrence. Accurate forecasts, relying solely on C.I. readings, had been made in 94.8% of 165 cancer follow-up patients. Nine patients with a poor cytological prognosis and no clinical signs of recurrence are still under observation. The cytological prognosis was incorrect in eight patients with persistent or recurrent disease and low C.I. readings. The possible causes of this prognostic error are discussed.

The technique of C.I. estimation is easy and can be learned in a short time. We suggest that C.I. estimations should be included in routine cytological cancer follow-up investigations in view of the important implication of this test.

My thanks are due to the British Empire Cancer Campaign for generous help with a grant from which much-needed technical laboratory assistance has been provided, enabling this work to be pursued. I also thank Professor J. C. McClure Browne for his continued encouragement and assistance with all aspects of the problems of cytology, aiding me with all the resources of the Institute of Obstetrics and Gynaecology.

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"Most foundation trustees and executive officers find themselves sooner or later involved in a discussion of the relative merits of small versus large grants. Large grants, of course, are more spectacular and in a way more satisfying because of the splurge they make. Then, too, a large grant avoids the temptation of scattering the foundation's shots too widely, with the possibility of dissipating the effectiveness of its program. Small grants have in their favor, especially for the smaller foundations, the advantage of helping in areas not covered by the large grants—areas where a relatively small amount of money will make a larger project of greater value."—1956-57 Annual Report of the John and Mary R. Markle Foundation, 511, Fifth Avenue, New York, 17.

SYSTEMIC SCLERODERMA WITH PORTAL HYPERTENSION

BY

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In systemic scleroderma ("progressive systemic sclerosis," Goetz, 1945), lesions of the hollow gastro-intestinal tract may occur at any site (Beigelman *et al.*, 1953; Cullinan, 1953; Leinwand *et al.*, 1954; Wiener, 1955; Piper and Helwig, 1955; Talbott and Ferrandis, 1956). Since, apart from one unelaborated report (Massimo, 1954), there appears to be no record of concurrent systemic scleroderma and portal hypertension, we describe here this association in two patients. Both had hepatic fibrosis, splenomegaly, and oesophageal varices with episodes of brisk haematemesis. One patient survived, following surgical relief of the effects of portal hypertension. The other, who had no operation on the portal system, died within one week of readmission to hospital for recurrent haematemesis.

Case 1

A housewife aged 31 was first admitted to St. James' Hospital for investigation in July, 1951. For two years she had felt increasing tightness of the fingers, which occasionally turned blue and cold. Although she had always been dark-skinned, pigmentation had increased in the past year. Her vitality, appetite, weight, mastication, and deglutition were all unimpaired. Menstruation was normal. The family, personal, and remote past histories were non-contributory.

Examination revealed an asthenic build (weight, 7 st. 8 lb.; 48.1 kg.), melanosis mainly sparing the face and not involving the mouth, contracture of the ocular, malar, and oral regions, and moderate sclerodactyly. The respiratory and cardiovascular systems were normal. The blood pressure was 120/85 mm. Hg. The liver and spleen were enlarged, each to about 2 cm. below the costal margin. There were no relevant neurological signs. The breasts and pubic hair appeared normal but the axillary hair was scant. No cataract, calcinosis circumscripta, telangiectasia, palmar erythema, or anterior abdominal collateral venous pattern was detected.

Investigations.—Haemoglobin level, 66% (9.8 g./100 ml.); erythrocyte count, 3,600,000/c.mm.; colour index, 0.91. The leucocyte and platelet counts were normal. The bone marrow was normoblastic. The E.S.R. was 68 mm. (Westergren) in one hour. The serum sodium, potassium, calcium, chloride, and inorganic phosphate values were normal. The blood urea was 41 mg./100 ml. Although the serum-bilirubin level was normal (0.2 mg./100 ml.), the results of other conventional hepatic tests were abnormal—that is, serum proteins, 8.75 g./100 ml. (albumin 4.15 g., globulin 4.6 g.); thymol turbidity, 15 units; and serum alkaline phosphatase, 30 K.A. units/100 ml. The 17-ketosteroid excretion was low (4.4 mg. a day). A skin biopsy showed the characteristic histology of scleroderma. The radiological findings were: chest, normal; barium swallow, incorporating the Trendelenburg position, normal;