An outstanding problem in the present case is the source of any immunization that may have occurred. The original antibody of Stratton and Renton resulted, like most known antibodies to antigens of the Rh series, from a straightforward immunization by a foetus which was subsequently born with haemolytic disease. In the present case the husband and surviving child lack the antigen; careful questioning has revealed no history of transfusion or injection of blood before the discovery of the antibody, or of any pregnancy by anyone but the husband. A spontaneous antibody would probably, however, unlike the present one, react better at 18° C. than at 37° C. and would not be greatly enhanced by albumin; a strong indirect anti-human-globulin test would, on the other hand, have been anticipated for an immune antibody.

One further piece of evidence that may have a bearing on the origin of the antibody is given by the serum Ga, which was discovered some years ago by Dr. M. M. Pickles and was at first thought to contain only anti-S. A recent investigation by Dr. R. R. Race shows that this serum also contains anti-C^x and anti-Mi^a. It is no longer possible to investigate the antigenic stimuli which may have given rise to these antibodies, but it may be that these two antibodies to rare antigens are, like anti-Wr^a, apt to arise without specific antigenic stimuli. We are indebted to Dr. Race for allowing us to mention these unpublished facts, which incidentally make the serum described in this paper the third example, not the second, of anti-C^x to be discovered.

The serum of Mrs. T. at first appeared to contain no abnormal antibody other than anti-C^x, but after the present paper had been written it was found to contain also an antibody against a rare antigen, possibly new, at present under investigation by Dr. M. Lauer, of Hamburg, and the staff of the Blood Group Reference Laboratory. A second serum containing the same antibody was found not to react with the cells of Mr. T. nor with those of three C^x-positives, including Mrs. W. In view of this finding it should be stated that all diagnoses of the C^x antigen mentioned in this paper were confirmed with the original anti-C^x serum of Stratton and Renton, which was shown not to contain the extra antibody.

Summary

A third example of the antibody anti-C^x is described, detected in the serum of an untransfused female patient in the course of compatibility tests performed prior to transfusion during surgical treatment for adenocarcinoma of the caecum. Details are given of serological tests on the red cells of the donor of the blood shown to be incompatible, and her family, together with those of comparative tests carried out with cells having a range of variants at the C locus (C, C^w, C^x, and c) and the corresponding antisera.

No source of immunization by pregnancy or injection of blood was established, and the antibody, despite some immune characteristics, was thought to be naturally occurring.

Our thanks are due to Dr. F. Kellett* and Mr. J. Clarke for their kind assistance and advice, and to Mr. D. K. Mulvany, the surgeon in charge of the case, for permission to investigate his patient.

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*Since this paper was written we have learned with deep regret of Dr. Kellett's sudden death on February 27, 1958.

Diabetes is the subject of the fifth *Conquest Pamphlet* issued by the Research Defence Society. The pamphlet answers in simple language common questions about the disease. Copies are obtainable from the society, 11, Chandos Street, Cavendish Square, London, W.1, price 6d. each.

MULTIPLE HETEROTOPIC SQUAMOUS-CELL CARCINOMAS

A CASE REPORT

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The purpose of this report is to record the occurrence in one patient of three heterotopic primary squamous-cell carcinomas and to discuss the case history in relation to modern views on multiple primary tumour formation.

Case Report

The patient, a housewife, was aged 71 years at the time of her death in April, 1957. Her father had died at the age of 70 of "cancer of the lung," but there was no other history of cancer in the family. The patient had never smoked more than two or three cigarettes a day, her alcohol consumption was negligible, and she had not lived abroad. Bilateral inguinal herniae were repaired when she was 50 years old. Since about this age she had had a winter cough productive of mucoid sputum, and this had always cleared up during the summer. She had had no other illnesses, and had received no radiotherapy until the appearance of her first carcinoma.

In August, 1948, she developed a nodule on the bridge of her nose. Shortly afterwards it ulcerated and she also noticed enlarged glands in the left side of her neck. She attended hospital four weeks after the appearance of the lesion. On examination she had koilonychia but no evidence of anaemia. On the skin of the bridge of the nose there was a circular ulcer a little less than 1 cm. in diameter, with raised firm edges; it was mobile over the deep structures, and lay just to the left of the midline. Two firm discrete lymph nodes in the upper left cervical group and the left pre-auricular lymph node were palpable. There was no other abnormal finding, and, in particular, the vocal cords were normal. Examination of the blood and urine showed no abnormality. Biopsy of the edge of the ulcer showed a moderately well differentiated squamous-cell carcinoma.

The lesion healed rapidly after superficial radiotherapy to a surface dose of 6,000 r at 90 kV applied over two weeks. The enlarged lymph nodes were removed by block dissection. No metastatic deposits were seen on microscopy of the excised nodes. The neck was therefore not irradiated.

In April, 1953, the patient complained of hoarseness of the voice of five months' duration. On indirect laryngoscopy the anterior part of the edge of the left vocal cord was slightly thickened. The epithelium was intact, the cords were mobile, but there were no enlarged cervical lymph nodes. The rest of the upper respiratory tract and the other systems were normal. The skin of the nose had healed. The blood Wassermann and Kahn reactions were negative. A radiograph of the paranasal air sinuses was normal. A chest radiograph showed bilateral apical pleural thickening and calcified foci in the right cardiophrenic, right hilar, and right paratracheal regions, but there was no evidence of recent or active pulmonary disease.

Over the next three months the lesion on the vocal cord was observed at frequent intervals, and it developed into a reddish sessile swelling on the anterior third of the left vocal cord. It did not ulcerate, and the cords remained mobile. Microscopy of tissue obtained by biopsy of this

swelling in June, 1953, showed a keratinizing squamous-cell carcinoma. In August the patient received teleradiotherapy to a tumour dose of 6,925 r over six weeks. In November her voice had improved and the vocal cords had healed, leaving a small white patch at the site of the carcinoma.

She remained well, apart from her winter cough, until February, 1957, when she was brought to the out-patient department because she had become slow in speech and movement, forgetful, and at times disorientated. On questioning she had had a cough with mucoid sputum, but no haemoptysis, for a few months, and she had had a vague continuous pain in the interscapular region for the previous two weeks. Her temperature was 96.2° F. (35.7° C.), and the pulse rate was 68 a minute and regular. She was slow-witted, but she could give a history and co-operate in the examination. No other abnormality was found and there was no recurrence of either of her previous carcinomas.

Three days later she was admitted to the ward, and on the day after admission complained of weakness in her left hand. Over the next week she developed a left hemiparesis with sensory loss of a cortical type in the left limbs. Nothing abnormal was found on examination of the chest, but a radiograph showed a large circular shadow behind the heart on the left side, and a smaller opacity in the left paratracheal region. Apart from an increased E.S.R. and an excess of protein in the cerebrospinal fluid, the results of laboratory investigation were not abnormal. The patient slowly became more drowsy and disorientated. She died in coma on April 22, 1957.

At necropsy (68 hours after death) there was no evidence of recurrence of the facial or laryngeal tumours. In the lungs terminal bronchitis was present and there were bilateral apical fibrous scars. The left lower lobe was almost replaced by necrotic neoplastic tissue, which appeared to originate in the left lower lobe bronchus. The mediastinal lymph nodes were greatly enlarged by secondary neoplastic tissue. A large metastatic deposit occupied the right temporo-parietal region, and a smaller one was present in the left occipital lobe. A benign polyp was found in the rectum, and there was a small benign endometrial polyp. There were no other significant abnormalities in any system.

Histology of the left lung revealed a poorly differentiated bronchogenic carcinoma of squamous type, with marked cellular and nuclear pleomorphism and many tumour giant cells. The cerebral deposits showed the same histological picture as the primary tumour.

Discussion

The interest of this case history lies in the occurrence of three primary squamous-cell carcinomas in one patient over a period of 10 years. Our assumption that these three growths were, in fact, all primary growths must first be justified. It is often stated that Billroth postulated three criteria to establish the existence of multiple primary tumours: (1) they must be histologically distinct, (2) they must arise in different sites, and (3) they must each produce separate metastases. We were unable to trace the source of this statement, but in 1887 Billroth and Von Winiwarter wrote that primary carcinomas might arise in two quite different sites, and that their independence could be demonstrated with complete certainty when the two carcinomas showed different histological structures. They went on to say that sometimes each of the primary tumours spread to lymph nodes and that in the metastases the characteristic form of each primary tumour could be found. This cautious expression of opinion on the subject is quite different from the very strict criteria usually attributed to Billroth.

In this patient all the tumours were of the same basic cell type, but we consider that their independence can be justified by their different sites of origin, by their clinical behaviour, and on histological differences.

The cutaneous and vocal cord lesions were each histologically primary carcinomas, continuity between normal and invasive squamous epithelium being visible. In the

tumour in the lung, continuity between normal and malignant epithelium was not demonstrable, but the microscopical appearances of the very poorly differentiated squamous carcinoma were characteristic of bronchogenic carcinoma. The central origin (Walter and Pryce, 1955) of the neoplastic mass also indicated a primary growth rather than a metastasis. The natural histories of the lesions support the histological findings because cutaneous and vocal cord epitheliomas rarely metastasize except to regional lymph nodes. The presence of cerebral metastases was likewise evidence that the lung lesion was a primary carcinoma.

The significance of the coincidence of these primary neoplasms must next be considered. All the lesions are in themselves common, and their fortuitous association in one patient is not impossible. The alternative explanation is that this patient was predisposed to malignant metaplasia of squamous epithelium. A review of the literature suggests that the last explanation is more likely to be the correct one.

Several authors have analysed series of patients with malignant neoplasms in an attempt to decide whether their incidence of multiple primaries was to be expected in a random distribution of cancer throughout the population. Warren and Gates (1932) and Bugher (1934), among others, concluded that multiple tumours occurred more often than would be expected. On the other hand, Peller (1941) thought that multiple cancer occurred less often than would be expected in a random distribution. The selection of cases, criteria for diagnosis, and methods of analysis varied widely in these reports, and this probably accounts for their differing conclusions.

Epstein and Shaw (1958) thought that a study of multiple neoplasms occurring in one particular system or tract would be more amenable to critical analysis than larger and more heterogeneous series. Out of 821 cases of primary carcinoma of the air and upper food passages they found 47 cases of multiple primary carcinoma; in 26 of these cases both primaries occurred in the air and upper food passages. The particular relationship between carcinoma of the bronchus and carcinoma of the larynx was emphasized by Cahan (1955), who studied 2,502 cases of carcinoma of the bronchus. Eighty-one of these patients suffered at one time from a neoplasm elsewhere in the body. This was in the larynx in 19 patients and the oral cavity in 18. From these reports it would appear that the frequency with which two neoplasms occur in the air and upper food passages is greater than would be expected in a chance distribution.

The probability that there was a systematic predisposition to carcinoma in this patient is increased by the sex incidence of the neoplasms, for all three are more common in males than in females. Intrinsic laryngeal carcinoma is over 13 times more common in males than in females (Curwen, Kennaway, and Kennaway, 1954), and squamous carcinoma of the skin is more than twice as common in males (Welton, Elliott, and Kimmelstiel, 1949). Carcinoma of the lung is five times more common in males (Registrar-General, 1955), and squamous-cell carcinoma of the bronchus has been reported to be 25 times more common in males (Moersch and McDonald, 1953).

The predisposition of large areas of tissue to neoplastic change is compatible with the theory of tumour formation put forward by Berenblum (1954). He views carcinogenesis as a long-drawn-out process consisting of two stages. Firstly, the tissue is initiated by the action of small amounts of specific carcinogen which converts a few normal cells into dormant tumour cells. The promotion of overt cancer in the initiated tissue is dependent on the exposure to non-specific factors, such as heat, light, or irritation, which would have no carcinogenic effects in tissue which had not been initiated. These views are supported by experimental evidence.

Discussing the environmental factors in the aetiology of cancer of the larynx, Wynder, Bross, and Day (1956) suggested that tobacco smoke might act as an initiating agent.

They also proposed that alcohol consumption acted as a promoter of carcinoma of the larynx.

It is reasonable to suppose that multiple primary tumours will occur with increasing frequency as the survival rate for cancer continues to improve with advances in diagnostic and therapeutic techniques. In this patient, for example, a complete cure of her skin and laryngeal carcinomas was effected by radiotherapy.

Summary

The case history is described of a woman who died at the age of 71 of a squamous-cell carcinoma of the bronchus after the successful treatment of two other squamous-cell carcinomas, on the face and on a vocal cord, in the last 10 years of her life.

From a review of the literature evidence is presented that suggests there was a systematic predisposition to cancer in this patient.

We acknowledge with thanks the interest and advice of Sir Daniel Davies. The patient had also been under the care of Miss G. Barry, Miss P. Wade, and Mr. J. D. McLaggan, and we are grateful to them for permission to publish this account.

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REPORT OF TWO CASES OF PRECOCIOUS PUBERTY

BY

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Precocious puberty is uncommon enough to warrant reporting. Various authors draw the line of precocity at different ages, but all are agreed that the onset of menstruation below the age of 8 is precocious, and in the two cases reported below menstruation began at the age of 5 and 2 respectively.

Precocity may be of cerebral, adrenal, or gonadal origin. Only where the origin is cerebral does true puberty occur—that is, development of secondary sex characters is accompanied by spermatogenesis or ovulation. Where the cause is adrenal or gonadal the testes or ovaries remain infantile and non-functioning.

Sex interest is uncommon in precocious children, but fertilization is possible in those of cerebral origin; for example, the case reported by Escomel (1939) of the Peruvian girl, Lina Medina, who first menstruated at 8 months, and at 5 years 8 months gave birth to a 6½-lb. (2,950-g.) boy.

Sexual precocity is usually associated with (1) greater physical activity—for example, the child walks early; (2) slight mental retardation with aggressiveness and bad temper—mental precocity is rare; (3) advanced skeletal development, giving an increase in height and weight, and an advance in the bone age with early closing of

the epiphyses—therefore such children are tall in childhood, but short in adult life; (4) undisturbed dentition; and (5) a late menopause.

In "cerebral" precocity the stimulus, which may be functional or organic, is directly on the brain, and is associated with an increase in the pituitary gonadotrophins which stimulate spermatogenesis or ovulation. Where the cerebral precocity is functional or "constitutional," as described by Jolly (1955), the puberty is normal in every way, but occurs many years too early. The normal order of events is maintained—that is, breast development first, then pubic hair, menstruation, axillary hair, and often a white leucorrhoeal discharge some months before the first menstrual period. The cases here reported belong to this group, and it is the most common cause of precocious puberty in girls. Genetic factors may play a part, but there was no hereditary history in these cases. The organic causes of cerebral sexual precocity are due to stimulation of the posterior part of the hypothalamus by tumour, meningitis, or encephalitis, with an intact pituitary, as the eosinophil cells must be free to secrete an excess of gonadotrophins and so stimulate the gonads. Weinberger and Grant (1941) suggest that the lesion of the posterior hypothalamus removes the normal control or inhibitory force exerted over the pars distalis of the anterior lobe of the pituitary, which then releases excess gonadotrophins that stimulate the ovaries or testes to produce oestrin or androgen, which in turn produce the secondary sex characters.

Non-cerebral precocity may be due to (1) adrenal tumours or hyperplasia; these usually produce virilism; or (2) ovarian tumours, the commonest of which is the granulosa-cell tumour, which, however, is very rare in girls under 10. Where it occurs the bleedings are anovular and the other ovary remains infantile, as it is not stimulated by the pituitary, and there are no gonadotrophins present. The tumour is usually large and palpable by the time the genitalia and breasts are affected, and the urinary oestrogens are higher than the normal adult level of 40–600 I.U. Other rare ovarian tumours which occasionally produce precocity are teratomas and chorionepitheliomas.

The following cases fall into the group of functional or constitutional cerebral precocity, and their interest lies in the differential diagnosis and management. The management of such cases after diagnosis should be, in the words of Morse (1897), "complete abstinence of all therapeutic measures, but the psychological treatment is important." The mother should be given a full explanation, and warned of the possibility of pregnancy, and the girl should be encouraged to "think of herself not as different from others, but as capable of growing up faster than her friends" (Jolly, 1955).

Case 1

This child was born by spontaneous delivery at full term on October 3, 1947. Birth weight was 6.12 lb. (2,775 g.). She was breast-fed for four months, and first walked at 11 months. Breast development was first noted at age 3. Three elder sisters were normal in development. No genetic factor was present in the family.

She was first brought to the gynaecological clinic by her mother on July 13, 1953, at the age of 5½ years, having had five days' vaginal bleeding two weeks previously. There was no pain and the child felt well. On examination she was an intelligent co-operative 5-year-old girl, tall for her age. The breast development was that of a 12-year-old