PLASMA STEROIDS AND NASOPHARYNGEAL CARCINOMA

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SYNOPSIS

The concentration of plasma dehydroepiandrosterone sulphate (DS), androsterone sulphate (AS) and cortisol have been measured in Chinese men living in Singapore. They were categorised as follows, (i) normal controls or ostensibly normal healthy subjects, (ii) patients with nasopharyngeal carcinoma, (iii) patients with cancer of other sites, and patients with either, (iv) patients severely ill with non-neoplastic diseases, and (v) patients with non-neoplastic diseases without constitutional symptoms. Each group was further divided into subjects 44 years of age and younger, and 45 years of age and older.

For the younger age group, the mean level of DS of the control group differed significantly from those of the clinical groups, although for AS, only the cancer groups differed from the control group. There were no differences in plasma cortisol levels between any of the groups. Plasma DS and AS levels were significantly lower in Chinese men with nasopharyngeal carcinoma than in normal controls but this is almost certainly a nonspecific effect of the disease, rather than a factor in the aetiology, since a similar abnormality was found in patients with cancer at other sites and, to a lesser extent, in severely ill patients with non-neoplastic diseases.

Studies in Kenya have suggested that endocrine abnormalities may be implicated in the aetiology of nasopharyngeal carcinoma (Clifford and Bulbrook, 1966; Wang *et al*, 1966; Bulbrook *et al*, 1968; Wang *et al*, 1968). Clifford and Bulbrook (1966) found that Kenyan men differed from British men in that they showed higher urinary excretion of total urinary oestrogens (oestrone, oestradiol-17β oestriol) and lower urinary excretion of 11-deoxy-17-oxosteroids such as dehydroepiandrosterone, androsterone and etiocholanolone; furthermore, Kenyans with nasopharyngeal cancer had significantly higher oestrogen: androgen ratios than normal controls. In a later investigation, Wang *et al* (1968) found that the plasma levels of dehydroepiandrosterone sulphate (DS) and androsterone sulphate (AS) were lower in Kenyan males than in British males; they also found that Kenyans with nasopharyngeal cancer had even lower plasma DS levels than control Kenyans although AS levels were similar.

The incidence of nasopharyngeal cancer in Kenya varies among the various tribal groups and while the highest recorded, 2·12 per 100,000 in Nandi males (Clifford, 1970), is somewhat higher than in Caucasian populations, it is much lower than in Southern China and in some of the peoples of South East Asia. The incidence of nasopharyngeal cancer in Singapore varies considerably among the major racial groups (Muir and Shanmugaratnam, 1967; Shanmugaratnam, 1967); the incidence among Chinese, Malay and Indian males was 18·5, 3·1 and 0·9 per 100,000 per year respectively during the period 1968-1970 (Shanmugaratnam, 1973).

It may be expected, therefore, that if endocrine abnormalities are important in the development of nasopharyngeal carcinoma, there would be obvious differences between the endocrine status of Chinese, Malay and Indian men. However, an investigation of the levels of plasma DS, AS, cortisol and transcortin in Chinese, Indian and Malay males in Singapore showed that the levels of these substances are the same for these racial groups (Wang *et al*, 1969). These findings provided no support for the hypothesis that an abnormal steroid environment in a particular population as evidenced by low plasma 11-deoxy-17-oxosteroid levels, is a necessary factor in the genesis of nasopharyngeal cancer.

However, low DS and AS levels were found in the few cases of nasopharyngeal cancer that were included in the previous study (Wang *et al*, 1969). This raised the possibility that cancer of the nasopharynx might occur more frequently in men with an abnormal hormonal environment, but a more likely explanation was that the subnormal plasma

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steroid levels represented a non-specific effect of the disease. We felt therefore that a comparison of plasma DS, and AS cortisol levels in Chinese men with nasopharyngeal carcinoma, with other cancers and other diseases may assist in explaining this finding.

MATERIALS AND METHODS

Subjects

Plasma was obtained between 8·30 a.m. and 11·30 a.m. from 5 groups of Chinese men in Singapore.

Group A: Normal Controls—healthy blood donors (91 cases)

Group B: Patients with nasopharyngeal carcinoma (26 cases)

Group C: Patients with cancers of other sites —mainly of the gastrointestinal tract and excluding cancers of the endocrine system and of organs associated with endocrine abnormalities (25 cases)

Group D: Patients with diseases other than cancer, mainly infections, associated with constitutional symptoms —a severely ill group (32 cases)

Group E: Patients with diseases such as haemorrhoids, cysts and uncomplicated hernias, without constitutional symptoms—a mildly ill group (27 cases)

Heparin was used as an anticoagulant. Plasma was stored at minus 70°C. The plasma samples were packed with solid carbon dioxide, flown to London and stored again at minus 20°C until assay.

Measurement of steroids

Plasma DS and AS were measured by the method of Wang *et al* (1968) except that Sephadex LH20 was used in place of celite (Vihko, 1966). All the results were expressed as ug. of the unconjugated steroid per 100 ml. plasma.

Plasma cortisol concentration was determined using a double isotope derivative method (James and Fraser, 1966).

RESULTS

The levels of plasma DS, AS and cortisol (or their urinary metabolites) in normal subjects are related to age (Borth *et al*, 1957; Deshpande and Bulbrook, 1964; Wang *et al*, 1968). The concentration of androgen sulphates rises rapidly at puberty and reaches a plateau in the third decade from which it then declines (Wang *et al*, 1968). Although urinary 17-hydroxycorticoids exhibit a similar rise and fall with age (Borth *et al*, 1957), plasma 17-hydroxycorticoids do not appear to change in concentration over the adult age range (Deshpande and Bulbrook, 1964). There is a large between-subject variation in the concentration of these steroids at all ages.

In the present study, the majority of the subjects were between 20-44 years of age. In this age range, plasma DS and AS levels reach a plateau and hence the correlation between steroid levels and age may be ignored. This can be seen in Fig. 1 where the plasma DS levels against age are shown; plasma AS would give the same pattern. From the age of 45 years onwards, there is an obvious fall in plasma DS and AS concentrations. We have, therefore, divided the subjects into two groups; those aged 44 years or less and those aged 45 years and above. This division gave mean ages which were the same for all the clinical groups investigated. There are very few controls in the older group and this, therefore, will not be considered further.

The mean concentration of plasma DS, AS (both expressed logarithmically) and cortisol for both age groups are shown in Fig. 2.

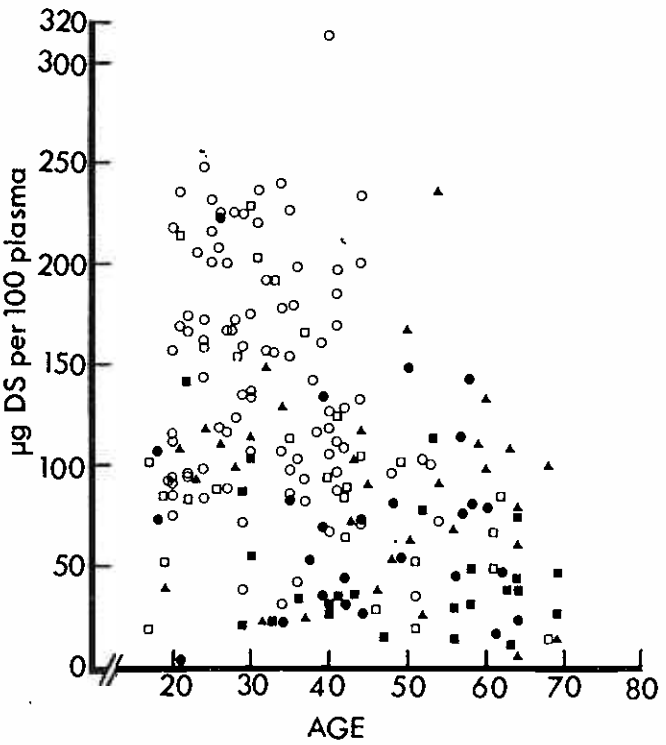

Fig. 1. The relationship between plasma dehydroepiandrosterone sulphate concentration and age.

The concentration of DS is expressed as ug of the non-sulphated steroid per 100 ml. of plasma. The figure includes control subjects (O), patients with nasopharyngeal cancer (●) and cancer at other sites (■), and patients with either moderate (□) or severe (▲) illnesses.

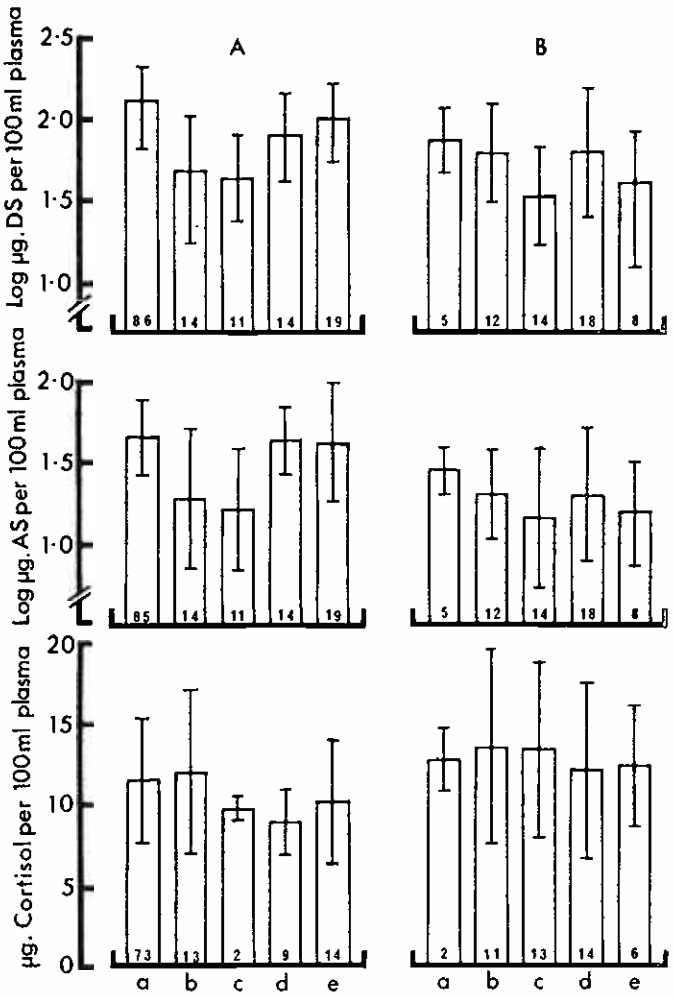

Fig. 2. Mean concentration of plasma steroids in various clinical groups of Chinese men.

The mean levels (ug/100 ml. plasma) and standard deviations of DS, AS and cortisol are shown as histograms; those on lefthand side (A) are subjects 44 years of age or younger and those on the righthand side (B) are 45 years or older. The order of the histograms are control subjects, (a); patients with nasopharyngeal cancer, (b); cancer of other sites, (c); patients with severe illnesses, (d); Patients with moderate illness, (e). The numbers in the histograms refer to the numbers of subjects in the groups.

TABLE I

RESULTS OF STUDENT "t" TEST ON GROUPS EXAMINED

(a) **Plasma dehydroepiandrosterone sulphate (DS)**

	NPC	Ca	S.	M.
Control	<0·001 (6·20)	<0·001 (7·25)	<0·001 (3·58)	<0·05 (2·07)
M	<0·02 (2·68)	<0·001 (3·70)	N.S.	
S	N.S.	<0·05 (2·44)		
Ca	N.S.			

Plasma DS: These levels are significantly subnormal in patients with nasopharyngeal cancer and subjects with cancers at other sites. Plasma DS levels were also significantly depressed in patients with other illnesses but to a lesser extent (see Fig. 2, Table I).

(b) **Plasma androsterone sulphate (AS)**

	NPC	Ca	S.	M.
Control	<0·001 (4·90)	<0·001 (5·58)	N.S.	N.S.
M	<0·02 (2·45)	<0·01 (2·94)	N.S.	
S	<0·02 (3·68)	<0·01 (3·53)		
Ca	N.S.			

Plasma AS: The results of estimations of plasma AS were similar to those of DS, in that the mean levels in both cancer groups were significantly lower than that of the normal controls and both groups of ill patients. The AS concentrations of patients with other illnesses did not differ from that in the normal controls (see Table I).

Abbreviations refer to the following Groups:

NPC —Patients with nasopharyngeal cancer.

Ca —Patients with cancer at other sites.

S —Severely ill patients with diseases other than cancer.

M —Moderately ill patients with diseases other than cancer.

Control —Healthy blood donors.

The first number is the probability (P) and the number in brackets is the value of "t".

Plasma Cortisol: The mean cortisol values ranged from 9 to 12 ug. per 100 ml. plasma in all five categories and do not differ from each other significantly.

DISCUSSION

Plasma androgen sulphate concentrations are considerably lower in Chinese men with nasopharyngeal cancer than in normal controls; but the results of this paper indicate that this is almost certainly a non-specific effect of the disease since a similar abnormality was found in patients with cancer at other sites. There is an extensive literature to the effect that a wide variety of diseases are

associated with low 17-oxosteroid excretion (Chou and Wang, 1939; Forbes *et al*, 1947). Our own results are in agreement with these findings.

There is, however, one caveat. Many patients with breast cancer also excrete sub-normal amounts of 11-deoxy-17-oxosteroids and have sub-normal levels of plasma DS and AS even at the earliest clinical appearance of the disease. These steroid abnormalities are highly correlated with the subsequent clinical course of the disease and it has been suggested that the steroid levels are simply a reflection of the severity of the disease (Bulbrook, 1970). However, the preliminary results of a prospective study in which urinary androgen metabolites were measured in ostensibly normal women indicated that sub-normal amounts of these metabolites precede the clinical appearance of the disease (Bulbrook and Hayward, 1967; Bulbrook, 1967). It appears that this abnormality becomes more marked as the disease progresses.

It seems highly improbable that a similar underlying abnormality is present in nasopharyngeal cancer, although it is not possible to come to any decision on this point from our present results. An answer could be obtained from a prospective study in which the steroids were measured in a normal Chinese population before the development of nasopharyngeal cancer.

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