Studies of plasma zinc, copper, caeruloplasmin, and growth hormone
With special reference to carcinoma of the bronchus

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SUMMARY The levels of plasma zinc, copper, caeruloplasmin, and growth hormone were determined in a group of normal people and in four groups of patients who were suffering from carcinoma of the bronchus, other forms of malignancy, chest illnesses, and diseases other than chest illness or malignancy. The plasma zinc was higher, and the plasma copper lower, in people without malignancy below the age of 30 years than they were in other age groups.

It was confirmed that about 66% of patients with carcinoma of the bronchus had plasma zinc levels less than 11.5 µmol/l but low levels were also found in 23% of other cases of malignancy and in 9% of the other patients. In carcinoma of the bronchus the low plasma zinc was found to be associated with epidermoid and anaplastic tumours and was to some extent related to the duration of the disease.

In carcinoma of the bronchus the plasma copper was found to be higher than in all other groups, and values higher than 26.5 µmol/l were considered to support a diagnosis of carcinoma of the bronchus. There was, however, no relationship between the increase in the plasma copper and the decrease in the plasma zinc.

Raised caeruloplasmin levels above 420 mg/l were found in 65% of cases of carcinoma of the bronchus, and these high levels were usually associated with raised plasma copper. Growth hormone was normal in all groups except six patients with carcinoma of the bronchus with secondary carcinoma of the liver, in whom it was raised. Surgical operations lowered plasma zinc and raised growth hormone but did not affect plasma copper.

A plasma zinc below 11.5 µmol/l is helpful in the diagnosis of carcinoma of the bronchus, but by itself it is not sufficiently specific to be considered diagnostic or to form a reliable screening test. A raised plasma copper and a raised plasma caeruloplasmin were useful supportive findings.

In 1968 Davies et al. investigated the level of plasma zinc and reported that, in adults, it was remarkably uniform in both health and certain diseases. There was, however, a significant lowering of the zinc level in some forms of malignant disease, superficial skin ulceration, and some cases of cirrhosis of the liver. They also found a significant but temporary lowering of the plasma zinc after the administration of glucose, either by mouth or intravenously, and this effect they attributed to an increased metabolism of zinc.

Their investigation into plasma zinc levels in 81 cases with malignant disease showed a striking decrease in plasma zinc in carcinoma of the bronchus compared with normal and with most other types of malignancy. They found that the majority of cases of carcinoma of the bronchus had zinc levels below 11.5 µmol/l (75 µg/dl) whereas patients with other carcinomata seldom had levels as low as this.

Davies et al. pointed out that the introduction of the atomic absorption spectroscopy method had made available a rapid and reliable technique which allowed reassessment of previously published work using other methods. Many authors have supported the finding of low plasma zinc levels in bronchial carcinoma but have also reported low levels in a large number of other conditions, such as liver disorders, myocardial infarction, Down's syndrome, indolent skin ulcers, cystic fibrosis of the pancreas,

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pregnancy and use of oral contraceptives, and even in chest infections, including active tuberculosis (Halsted and Smith, 1970; Morgan, 1970; Sinha and Gabrieli, 1970; Andrews, 1971; Strain et al., 1972; Beeley et al., 1974; McBean et al., 1974). These findings appear to render an estimation of the plasma zinc of little clinical value except in certain limited conditions. Nevertheless Davies (1972) reconfirmed the value of persistently low plasma zinc levels in the diagnosis of carcinoma of the bronchus, especially in those patients with metastases, and thought that this was sufficiently characteristic to distinguish carcinoma of the bronchus from other carcinomata.

Zinc is essential for growth and development and appears to be particularly related to squamous epithelium. Low plasma concentrations have been found in burned patients (Cloutier et al., 1971; Larson et al., 1971), and oral zinc sulphate therapy has improved healing in wounds, skin ulcers, and burns (Pories et al., 1967; Husain, 1969; Greaves and Skillen, 1970; Serjeant et al., 1970; Hallböök and Lanner, 1972). It is possible that the low zinc levels in carcinoma of the bronchus could be related to the type of epithelium from which the tumour is derived, although previous reports suggest that a zinc deficiency is responsible for poor epithelial growth rather than excessive growth.

It is desirable to discover the reason for the link between zinc and carcinoma of the bronchus, and following our earlier observations (Andrews, 1971) we have continued our studies with several aims in view: firstly, to see if the relationship is specific and is a byproduct of tumour metabolism, or if it gives an indication of a change in the patient’s metabolism which allows the tumour to grow; secondly, to see if there was a relationship between the lowering of plasma zinc and the nature of the tumour epithelium and the size of the tumour, as judged by the presence of metastases or the duration of the disease, which could point to zinc being more specifically related to tumour tissue. Also, low plasma zinc levels in normal people and in patients suffering from other conditions might indicate a group of people susceptible to carcinoma of the bronchus or provide a cross-link between diseases of other organs involving similar epithelia.

Because it has been suggested that, in certain circumstances, trace elements can become inter-changeable in the body (Morgan, 1970; Pfeiffer et al., 1971), a parallel study was carried out on plasma copper. At the time this was started there had been few studies of the plasma copper in malignancy. Pagliardi and Giangrandi (1960) had reported raised plasma copper levels in Hodgkin’s disease, and this was confirmed by Jensen et al. (1964).

Sinha and Gabrieli (1970) reported a raised serum copper in many conditions other than malignancy and considered the change to be of little diagnostic value.

When it became obvious that the plasma copper results were unusual, the role of caeruloplasmin in carcinoma of the bronchus and other malignancies was also investigated to see if the levels of this copper oxidase in plasma altered in malignancy, and whether or not the change, if any, was related to the levels of plasma copper.

The endocrine effects of some bronchial tumours are well known although it is not always entirely clear how some of these effects are produced. It was decided to investigate the levels of growth hormone in cases of carcinoma of the bronchus and to compare these levels with those found in other groups of patients to see if growth hormone had any specific connection with carcinoma of the bronchus or had any apparent influence on the level of zinc in these cases.

Material and methods

ZINC AND COPPER
Plasma zinc and copper estimations were performed on the Unicam SP90 Atomic Absorption Spectrophotometer by the standard methods using propane gas as the fuel gas and air as the oxidiser.

CAERULOPLASMIN
Caeruloplasmin was estimated in plasma using the single radial immunodiffusion plate (M-partigen) supplied by Hoechst Pharmaceuticals. Each test plasma was diluted 1:2 with physiological saline and 5 μl was applied to the well in the immunodiffusion plate. Diffusion time was 48 hours at room temperature. The assay range of the plate is 30-300 mg/l so that further dilution of the plasma with physiological saline and a repeat estimation were sometimes necessary.

GROWTH HORMONE
Growth hormone (HGH) was estimated by radioimmunoassay using a kit manufactured by CEA-IRE-SORIN. This is a double antibody technique with addition of human albumin to assist precipitation. The normal adult basal level by this method is <1.0-5.0 μg/l.

CLINICAL MATERIAL
The estimations were carried out on the following groups of people.

Group A
Normal people between the ages of 10 and 69 years,
free from any disease as far as was known. These included laboratory and other staff.

**Group B**

Patients over the age of 10 years, suffering from a wide variety of disease other than pulmonary disease or malignancy. Among these were heart disease (including angina but without evidence of acute myocardial infarct), hypertension, diabetes mellitus, sarcoid, cyst of liver, anaemias, hereditary telangiectasia, arthritis, hiatus hernia, and influenza.

**Group C**

Patients over the age of 10 years, suffering from pulmonary disease other than malignancy. These included bronchitis, emphysema, pneumoconiosis, and asthma.

**Group D**

Cases of carcinoma of the bronchus.

**Group E**

Adult cases of malignancy other than carcinoma of the bronchus.

**Group F**

Adult patients undergoing surgical operation for malignancy other than carcinoma of the bronchus.

**Group G**

Adult patients undergoing surgical operation and not suffering from a malignant condition.

**Results**

**ZINC AND COPPER**

The zinc and copper results for groups A, B, C, D, and E are shown in Table 1. It will be seen that in each group the results cover a wide range and that groups A, B, and C are very similar to each other. However, the carcinoma of the bronchus group is significantly different from all the others in that the zinc levels are lower and the copper levels are higher (p <0-001 in all comparisons for both zinc and copper).

The zinc levels in patients suffering from malignancy other than carcinoma of the bronchus (group E) were also significantly lower than those of patients suffering from chest and other diseases (groups C and B) but not different from those of normal people. The copper levels for patients suffering from malignancy, other than carcinoma of the bronchus, were significantly higher (p <0-01) than for all other groups except the carcinoma of the bronchus group.

If the results of groups A, B, and C are combined and arranged in age groups, as in Table 2, it will be seen that the zinc levels in patients under the age of 30 are higher than in the other groups, the difference being significant in the groups between the ages of 30 and 69 years but only approaching significance when compared with the group over 70 years. The copper levels are significantly lower in patients under the age of 30 when compared to all other groups.

Davies et al. (1968) suggested that a plasma zinc of 11-5 µmol/l (75 µg/dl) or lower was highly suggestive of carcinoma of the bronchus. In this series 54 (66-67%) of 81 cases of carcinoma of the bronchus had zinc levels below 11-5 µmol/l. In the other groups 18 (9%) of 198 of the patients who were normal or suffering from chest or other illnesses, and 19 (23%) of 82 cases of other types of malignancy had zinc levels below 11-5 µmol/l.

The significant elevation of the copper levels in cases of carcinoma of the bronchus prompted a search for a copper value which might have a similar

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**Table 1** Plasma zinc and copper levels in normals (group A), illnesses other than malignancy or pulmonary disease (group B), pulmonary disease other than malignancy (group C), carcinoma of the bronchus (group D), and other types of malignancy (group E)

<table>
<thead>
<tr>
<th>Group</th>
<th>Plasma zinc (µmol/l)</th>
<th>Plasma copper (µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>A</td>
<td>11-0 — 18-5</td>
<td>14-48 ± 1-96</td>
</tr>
<tr>
<td>B</td>
<td>10-75 — 20-8</td>
<td>14-82 ± 2-44</td>
</tr>
<tr>
<td>C</td>
<td>9-8 — 17-75</td>
<td>14-73 ± 2-68</td>
</tr>
<tr>
<td>D</td>
<td>5-5 — 18-35</td>
<td>10-97 ± 2-35</td>
</tr>
<tr>
<td>E</td>
<td>6-1 — 27-8</td>
<td>13-69 ± 3-28</td>
</tr>
</tbody>
</table>

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**Table 2** Plasma zinc and copper levels in all patients, other than those suffering from malignancy, arranged in age groups

<table>
<thead>
<tr>
<th>Age group</th>
<th>Plasma zinc in groups A, B, and C (Mean ± SD) (µmol/l)</th>
<th>Plasma copper in groups A, B, and C (Mean ± SD) (µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10—29</td>
<td>15-83 ± 2-57</td>
<td>17-93 ± 4-51</td>
</tr>
<tr>
<td>30—49</td>
<td>14-75 ± 2-77</td>
<td>20-57 ± 4-81</td>
</tr>
<tr>
<td>50—69</td>
<td>14-35 ± 2-36</td>
<td>20-78 ± 3-45</td>
</tr>
<tr>
<td>70+</td>
<td>14-75 ± 1-73</td>
<td>21-04 ± 3-57</td>
</tr>
</tbody>
</table>

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significance to the 11·5 \( \mu \text{mol/l} \) zinc value. It was found that 53 (65·4\%) of the 81 cases of carcinoma of the bronchus had copper values higher than 26·5 \( \mu \text{mol/l} \). Only 12 (6\%) of the 198 normal people and those suffering from chest illnesses and other illnesses apart from malignancy, and 16 (19\%) of the 82 patients suffering from malignancy other than carcinoma of the bronchus had copper levels above 26·5 \( \mu \text{mol/l} \).

Thirty-eight (47\%) cases of carcinoma of the bronchus had both a plasma zinc of less than 11·5 \( \mu \text{mol/l} \) and a plasma copper greater than 26·5 \( \mu \text{mol/l} \).

There was, however, no correlation (correlation coefficient = 0·1) between the fall in the zinc value and the rise of the copper value in patients with carcinoma of the bronchus. The two elements, therefore, did not appear to be directly related to each other.

Assuming that the presence of secondary deposits could be taken to indicate the size of the tumour tissue, and possibly an indication of rate of growth, the cases of carcinoma of the bronchus were divided into 52 patients without secondary deposits and 29 patients with secondary deposits of carcinoma.

Those without secondary deposits had a mean plasma zinc level of 11·05 \( \mu \text{mol/l} \) with a standard deviation of 2·48, and a mean plasma copper level of 27·7 \( \mu \text{mol/l} \) with a standard deviation of 4·49.

Those with secondary deposits had a mean plasma zinc level of 10·8 \( \mu \text{mol/l} \) with a standard deviation of 2·13, and a mean plasma copper level of 27·7 \( \mu \text{mol/l} \) with a standard deviation of 4·73.

Clearly there is no significant difference between the levels in these two groups.

The length of history given by patients suffering from carcinoma of the bronchus was recorded, where this was possible with reasonable accuracy, and the results are shown in Table 3. There is an apparent fall in the means of the zinc values and a possible increase in the means of the copper values the longer the disease has been present, but the differences are not significant.

It was only possible to grade the bronchial carcinomata histologically with certainty in a relatively small number of cases. These are shown in Table 4. It will be seen that there is a significant difference in the zinc values between epidermoid carcinoma and oat-cell tumours \((t = 1·91; P = 0·05)\) and epidermoid and adenocarcinomata \((t = 2·03; P = 0·05)\) but not between epidermoid carcinomata and anaplastic tumours. There is no significant difference between the copper values in the four groups.

In view of the fact that the low zinc levels appeared to be specially related to epidermoid carcinoma,

<table>
<thead>
<tr>
<th>Duration of lesion in series</th>
<th>Number of plasma zinc and copper compared with duration of illness in cases of carcinoma of bronchus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma zinc (Mean ± SD) ( \mu \text{mol/l} )</td>
</tr>
<tr>
<td>1--3mth</td>
<td>17</td>
</tr>
<tr>
<td>4--6mth</td>
<td>18</td>
</tr>
<tr>
<td>7--12mth</td>
<td>12</td>
</tr>
<tr>
<td>1--3yr</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 4  Comparison of plasma zinc and copper found in different histological types of carcinoma of bronchus

<table>
<thead>
<tr>
<th>Type of carcinoma</th>
<th>Number in series</th>
<th>Plasma zinc (Mean ± SD) ( \mu \text{mol/l} )</th>
<th>Plasma copper (Mean ± SD) ( \mu \text{mol/l} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermoid</td>
<td>21</td>
<td>10·12 ± 2·49</td>
<td>27·5 ± 4·82</td>
</tr>
<tr>
<td>Oat-cell</td>
<td>8</td>
<td>11·47 ± 1·27</td>
<td>26·07 ± 4·03</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5</td>
<td>14·43 ± 4·59</td>
<td>26·76 ± 5·58</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>9</td>
<td>10·98 ± 0·94</td>
<td>29·00 ± 3·94</td>
</tr>
</tbody>
</table>

An analysis of this small group was carried out. This showed that there was no significant difference between the zinc levels of those with or without secondary deposits. There was, however, a fall in plasma zinc and also a rise in plasma copper as the duration of lesion increased, but in view of the small numbers and the variation in values it was felt that no definite conclusion could be drawn.

In 15 cases of carcinoma of the bronchus it was possible to follow the plasma zinc at regular intervals for three to four months. In seven cases the plasma zinc level fell, and in four of these the level fell from above 11·5 \( \mu \text{mol/l} \) to below that level; in the other three the plasma zinc was already below 11·5 \( \mu \text{mol/l} \). In seven cases the zinc level remained more or less the same. Three of these were above the 11·5 \( \mu \text{mol/l} \) level and the other four were below it. In the other case the plasma zinc level rose from 10·4 to 13·15 \( \mu \text{mol/l} \) after deep x-ray therapy.

The group of patients with malignant tumours other than carcinoma of the bronchus (group E) contained a wide variety of tumours and included single cases of reticulum cell sarcoma, mesothelioma, seminoma, melanoma and carcinomata of the bladder, larynx, oesophagus, skin, small intestine, thyroid, and vulva and two cases each of lymphosarcoma, Hodgkin's disease, and carcinoma of the corpus uteri. In this small group the plasma zinc was below 11·5 \( \mu \text{mol/l} \) in the two lymphosarcomata, in one of the cases of Hodgkin's disease, and in the single cases of carcinoma of the bladder, oesophagus, thyroid, and vulva. The plasma copper levels were all below 26·5 \( \mu \text{mol/l} \).

The remaining cases in group E have been grouped
according to the site of the primary tumour, and the zinc and copper levels are shown in Table 5. There is no statistical difference between the groups, although the variation within the groups is quite considerable. Carcinoma of the cervix, a tumour of squamous epithelium, has a relatively high mean figure for zinc. Among these tumours a plasma zinc below 11-5 μmol/l was found in four cases of carcinoma of the breast, four cases of carcinoma of the stomach, and one case of carcinoma of the cervix, pancreas, prostate, and rectum. A plasma copper above 26-5 μmol/l was found in five cases of carcinoma of the cervix, three cases of carcinoma of the breast, two cases of carcinoma of the stomach, two cases of carcinoma of the colon, and one case each of carcinoma of the pancreas, prostate, and small intestine.

Table 5 Plasma zinc and copper levels in majority of other malignant cases (group E) grouped according to site of primary tumour

<table>
<thead>
<tr>
<th>Primary site of carcinoma</th>
<th>Number of patients</th>
<th>Plasma zinc (Mean ± SD) (μmol/l)</th>
<th>Plasma copper (Mean ± SD) (μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>10</td>
<td>12.81 ± 3.97</td>
<td>20.68 ± 5.51</td>
</tr>
<tr>
<td>Colon</td>
<td>7</td>
<td>13.72 ± 1.45</td>
<td>24.46 ± 4.03</td>
</tr>
<tr>
<td>Rectum</td>
<td>5</td>
<td>12.23 ± 0.94</td>
<td>21.53 ± 3.09</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4</td>
<td>14.07 ± 3.3</td>
<td>25.34 ± 3.3</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>16.71 ± 7.9</td>
<td>26.05 ± 6.99</td>
</tr>
<tr>
<td>Breast</td>
<td>16</td>
<td>13.77 ± 2.94</td>
<td>24.34 ± 4.58</td>
</tr>
<tr>
<td>Cervix</td>
<td>19</td>
<td>15.11 ± 2.62</td>
<td>23.57 ± 5.12</td>
</tr>
</tbody>
</table>

A combined low plasma zinc and raised plasma copper was found in single cases of carcinoma of the breast, pancreas, prostate, and stomach.

CAERULOPLASMIN

Carcinoma, copper, and zinc were estimated on the plasma of 19 normal controls, 58 cases of carcinoma of the bronchus, and 55 cases of other carcinomata. These were considered separately from the rest of the series. The mean values and standard deviations of the plasma caeruloplasmin for these groups are shown in Table 6. It will be seen that in the carcinoma of bronchus group the caeruloplasmin is significantly higher than in the control group \( t = 6.83; \ p < 0.001 \) and the other carcinoma group \( t = 4.33; \ p < 0.001 \). In the latter, all types of carcinoma showed similar values.

This special group of carcinoma of the bronchus contained a high proportion of patients in whom the plasma copper was raised above 26-5 μmol/l, and the caeruloplasmin values of those with or without a raised plasma copper are also shown in Table 6. There is a significant difference between these two groups \( t = 5.3; \ p < 0.001 \) and clearly there appears to be, perhaps not surprisingly, an association between copper and caeruloplasmin. The fit is not exact, however, and the correlation coefficient was 0.7.

The caeruloplasmin results were examined to see if there was a critical level similar to the 11-5 μmol/l for zinc and 26-5 μmol/l for copper. Histogram studies revealed that 420 mg/l was a reasonable and useful level to adopt. Thirty-eight (65%) of the 58 cases of carcinoma of the bronchus had caeruloplasmin levels of 420 mg/l and above, compared to only one of the normal controls and 15 (27%) of the other carcinoma group.

Considering this special group of 58 cases of carcinoma of the bronchus alone, if the three criteria of low plasma zinc, raised plasma copper, and raised plasma caeruloplasmin are used together in assessing the diagnosis, 54 (93%) patients had one or more of these abnormal parameters. All three parameters were abnormal in 26; two parameters were abnormal in 16 (11 raised caeruloplasmin and raised copper; 4 raised copper and lowered zinc; and 1 raised caeruloplasmin and lowered zinc) and in 12 patients only one parameter was abnormal (7 with low plasma zinc and 5 with raised plasma copper).

HUMAN GROWTH HORMONE

In all except six cases of carcinoma of the bronchus the growth hormone level was below 5 μg/l, the upper limit of our normal range. The level did not appear to be related in any way to the histological type of the tumour or to the duration of the illness. In the six other cases the levels were raised, sometimes considerably; these were 23-4, 9-45, 31-5, 26-5, 10-8, and 7-5 μg/l respectively. All of these had secondary deposits of carcinoma in the liver, diagnosed either by direct observation or on clinical evidence supported by diagnostic biochemistry tests. No other common factor which might explain the raised HGH in these six cases could be determined. The presence or absence of pulmonary osteoarthropathy was not recorded.

EFFECT OF SURGICAL OPERATIONS

Because it became apparent that both the zinc and copper results were covering a wide range and that
patients, particularly those with carcinomata other than carcinoma of the bronchus, had plasma zinc levels below the level of 11·5 μmol/l, an attempt was made to see if any explanation for these unexpected low levels could be found. Since the majority of our patients were hospital inpatients, the possibility of a hospital procedure such as a surgical operation influencing the plasma level was considered. Two separate series of cases were investigated, one composed of 11 cases of carcinomata other than carcinoma of the bronchus, and the other composed of 37 patients suffering from illnesses other than carcinomata, who were all undergoing a surgical operation. The plasma zinc and copper were estimated in these patients both before and after the surgical operation, and in all but two patients in each series, the growth hormone was similarly estimated.

The carcinoma groups consisted of cases of carcinoma of the breast, ovary, thyroid, cervix, stomach, larynx, and rectum. The other group consisted of gynaecological operations, cholecystectomies, proctectomies, simple thyroidectomies, resections of bowel, herniae, and lumbar sympathectomy.

The results are summarised in Table 7. It will be seen that the plasma zinc falls after a surgical procedure, although this is significant only in the carcinoma series \( t = 2·19 \); \( 0·05 > p > 0·02 \). It may be that this is related to the extent of the surgical procedure, on the assumption that carcinoma operations usually involve a greater removal of tissue than other operations. On the other hand, the preoperation mean zinc level of the non-carcinoma group is surprisingly low.

The surgical procedures apparently have no significant influence on the copper levels.

All the preoperation levels for HGH in both groups were within the normal range except in one patient with Crohn’s disease, in whom the level was raised to 8·4 μg/l. Although the figures are not entirely satisfactory, it will be seen that there is a postoperative rise in the level of growth hormone in both groups. This rise is statistically significant in the non-carcinoma group \( t = 2·85; p < 0·01 \) and also approaches significance in the carcinoma group.

Discussion

Davies et al. (1968) considered that a low plasma zinc was characteristic of patients with carcinoma of the bronchus and that 11·5 μmol/l (75 μg/dl) could be regarded as a critical level, the majority of patients with carcinoma of the bronchus having levels below this. The present series has confirmed 11·5 μmol/l as a useful figure which could assist in the diagnosis of a doubtful case of carcinoma of the bronchus. Unfortunately, however, it cannot be considered to be diagnostic, or sufficiently clearcut to provide an effective screening test. A low plasma zinc can be found in every type of case and even in apparently normal people. One of our normals had a plasma zinc below 11·5 μmol/l but it was later ascertained that this person had been investigated for a possible pulmonary lesion some years previously, although no abnormality was discovered. There were three patients with a low plasma zinc in those suffering from conditions other than pulmonary illness or malignancy (group B); these were cases of hay fever, sarcoidosis, and rheumatoid arthritis. In the pulmonary disease group (group C) there were 14 patients with a low plasma zinc; these included five patients who had previously suffered from pulmonary tuberculosis and were being kept under observation; seven cases of bronchitis, one of whom had had haemoptysis; one case of bronchiectasis; and one case of cystic lung. Some of these cases have been followed for many years and, so far as is known at present, none of these has developed carcinoma of the bronchus.

One patient in the carcinoma of bronchus group originally had a plasma zinc of 11·5 μmol/l. Tuberculosis was diagnosed and, under treatment, the plasma zinc rose to 13·15 μmol/l. Four years later the patient again reported with chest illness, and at that time the plasma zinc was 12·35 μmol/l. Two months later carcinoma of the bronchus was diagnosed and the plasma zinc was then 9·8 μmol/l. Apart from this one case, which is open to several interpretations, there was nothing to suggest that a low plasma zinc indicates a susceptibility to carcinoma of bronchus.

Table 7  Effect of surgical operations on plasma zinc, copper, and growth hormone

<table>
<thead>
<tr>
<th>Group undergoing surgical operation</th>
<th>Plasma zinc (Mean ± SD) (μmol/l)</th>
<th>Plasma copper (Mean ± SD) (μmol/l)</th>
<th>Plasma HGH (Mean ± SD) (pg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma Pre-op</td>
<td>13·07 ± 2·6</td>
<td>20·02 ± 4·31</td>
<td>1·06 ± 0·96</td>
</tr>
<tr>
<td>Carcinoma Post-op</td>
<td>10·63 ± 2·62</td>
<td>20·83 ± 4·87</td>
<td>2·85 ± 3·5</td>
</tr>
<tr>
<td>Non-carcinoma Pre-op</td>
<td>11·97 ± 2·12</td>
<td>20·3 ± 5·4</td>
<td>0·86 ± 1·47</td>
</tr>
<tr>
<td>Non-carcinoma Post-op</td>
<td>10·97 ± 3·32</td>
<td>21·94 ± 4·9</td>
<td>2·33 ± 2·75</td>
</tr>
</tbody>
</table>

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The wide scatter of low plasma zincs throughout all the groups was obviously against zinc playing a specific role in carcinoma of the bronchus or even in malignancy in general, but it could be related to altered tissue metabolism, possibly associated with tissue destruction. The facts that the duration of the bronchial carcinoma appeared to contribute to the lowering of the plasma zinc and that low plasma zincs were more common in other forms of malignancy and after surgical operations, particularly after the more extensive carcinoma operations, support the suggestion that tissue destruction may be a basic cause. The low postoperative plasma zinc also underlines the need to consider all facts relevant to the patient when attempting to interpret the significance of biochemical results.

A low plasma zinc could be the result of a deficiency caused by a concentration of zinc near the tumour site, as occurs at wound margins (Savlov et al., 1962), and in these circumstances the zinc might be needed for normal tissue growth in repair and defence mechanisms. Griffith et al. (1973) considered increased tissue zinc to be an indication of the body’s defences in malignancy and not a reflection of premalignant change or poor nutritional state. The present findings support the suggestion that the low plasma zinc is the direct effect of the presence of a tumour, in which case oral zinc sulphate might increase the body’s defence against the tumour.

The apparent connection between the low plasma zinc and the epidermoid type of bronchial carcinoma was interesting in view of the previously published work indicating zinc deficiency in severely burned patients and the beneficial effect of zinc sulphate on the healing of burns and other wounds. Zinc may have some special part to play in the metabolism of squamous epithelium, and it is probable that the anaplastic group of bronchial carcinomata, the other histological group to show a consistently low plasma zinc, contained anaplastic epidermoid tumours. In the group of other carcinomata, however, it was not possible to relate a low plasma zinc to any specific type of tumour, and it is surprising that the carcinoma of cervix group contained only one patient with a low zinc.

The finding of a high plasma copper in carcinoma of the bronchus adds another valuable diagnostic procedure to the investigation of such cases. Strain et al. (1972) reported high copper levels in many types of carcinoma, including 12 cases of carcinoma of the bronchus, although in these patients the zinc was normal, and Sinha and Gabrieli (1970) reported a raised plasma copper in many conditions and considered the estimation to be of doubtful value in diagnosis. Our findings do not agree with this and, since we began our work, other papers have appeared which have reported results somewhat similar to our own. Kotaric et al. (1975) found serum copper levels above 165 μg/dl (25-9 μmol/l) in 82 % of cases of carcinoma of the bronchus compared to 26-48 % in other cases of malignancy and concluded that a raised serum copper could be a diagnostic factor in carcinoma of the bronchus. Sirin et al. (1972) considered that blood copper levels could be used as a screening test in dysplasia and carcinoma of the cervix, values greater than 199 μg/dl (31-24 μmol/l) strongly suggesting invasive carcinoma. It now seems to be generally accepted that a raised plasma copper is commonly found in malignancy (Marczyńska et al., 1976; Light et al., 1977). As with the low plasma zinc, a raised plasma copper is not specific, but a value above 26-5 μmol/l strongly suggests a significant abnormality, and malignancy, especially carcinoma of the bronchus, should be carefully considered and excluded. It can be considered a useful supportive test in carcinoma of the bronchus.

The role of copper in metabolism and malignancy has not been extensively investigated except in anaemia and Kinnier-Wilson’s disease. Tani and Kokkola (1972) considered that in carcinoma of the bronchus a raised serum copper was directly related to a fall in serum iron and an increase in the size of the tumour. They also considered that a rise in serum copper was positively correlated with an increase in serum hexosamine which was brought about by the release of degradation products from the tumour (Kokkola and Tani, 1972).

So far as carcinoma of the bronchus is concerned, this present work did not disclose a relationship between the changes occurring in plasma zinc and copper, and in fact they appeared to be entirely independent of each other. However, it is possible that they have an underlying common cause in tissue destruction and release of degradation products by the tumour. We were unable to relate the zinc and copper levels to the size of the tumour although our attempts to assess this were crude, but there was a suggestion that the degree of both the fall in zinc and the rise in copper were related to the duration of the disease.

Raised levels of caeruloplasmin have been previously reported in malignancy. Schapira (1972) found caeruloplasmin raised in cases of carcinoma of the breast, cervix and vulva, and Shifrine and Fisher (1976) found raised levels in osteosarcoma. In both these papers attention is drawn to the fact that caeruloplasmin may also be increased by the action of hormones. Shifrine and Fisher correlated the raised caeruloplasmin to elevated copper levels which they found in osteosarcoma and in women.
taking the contraceptive pill. Their correlation was extremely good (correlation coefficient = 0.99) and led them to suggest that the copper:caeruloplasmin ratio is a constant, so that the estimation of one or other of the substances would be sufficient to disclose an abnormality. In the present series the correlation was not nearly so good, and of the 58 cases of carcinoma of the bronchus the normal ratio between caeruloplasmin and copper was disturbed by a high copper in 14 and by a high caeruloplasmin in 15, whereas in the other carcinomata groups the relationship was much closer. If this imbalance between plasma copper and caeruloplasmin should prove to be a significant feature of carcinoma of the bronchus, it obviously needs pursuing. Caeruloplasmin increases in inflammatory conditions, and the rise in both it and copper in carcinoma of the bronchus could be entirely non-specific, although we were unable to confirm the reported post-operative rise in plasma copper. On the other hand, the increases could be due to substances produced by the tumour. Caeruloplasmin is a copper containing amine oxidase which can catalyse the oxidation of some polyamines. Considerable interest in polyamines has been generated recently, particularly the role of putrescine, cadaverine, spermidine, and spermine in normal and neoplastic growth. The polyamines are apparently involved in RNA metabolism and are excreted in increased amounts by patients suffering from carcinoma (Marton et al., 1973; Lipton et al., 1975; Russell and Russell, 1975; Russell, 1977). An attempt to establish a relationship between increased plasma caeruloplasmin and an increased excretion of polyamines will form a basis for future work.

Increase in growth hormone levels in cancer patients has been reported by Solomon et al. (1974), and Pogosov et al. (1976) found increased levels in patients with carcinoma of the larynx undergoing radiation therapy. The mild postoperative increase in this present series can probably be explained by post-operative stress, and perhaps a mild degree of postoperative starvation could also have contributed. However, the relationship between carcinoma of the bronchus and hormone secretion has always aroused interest. Steiner et al. (1968) and Beck and Burger (1972), among others, have described increased secretion of growth hormone in cases of carcinoma of the bronchus, the increased secretion coming from the tumour itself. While the high levels found in our six cases could have been caused by tumour secretion, the apparent association with the presence of secondary deposits in the liver possibly suggests altered liver metabolism, such as changes in the amino acids. This finding needs further investigation.

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Studies of plasma zinc, copper, caeruloplasmin, and growth hormone

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Studies of plasma zinc, copper, caeruloplasmin, and growth hormone: With special reference to carcinoma of the bronchus

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