Europ. J. Cancer Vol. 11, pp. 365–371. Pergamon Press 1975 Printed in Great Britain.

Cancer and Altitude. Does Intracellular pH Regulate Cell Division?

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Abstract—*Tissue culture growth rate is very sensitive to changes in pH of the external medium (H. Eagle), suggesting that the concentration in cells of ^{+}H or ^{-}OH might be the key factor controlling synthesis and eventual mitosis in normal and cancerous tissue. Since physiological acclimatization to higher altitudes produces changes in alkali-reserve in man and animals remaining at altitude, a possible correlation with statistics on cancer has been investigated.*

Available data on registrations of cancer (International Committee Against Cancer) and of cancer deaths (World Health Organization) have been analyzed for possible correlation of age-specific rates with a population-weighted mean altitude for each region surveyed. There is no "altitude-effect" below 60 or 65 years, but a statistically significant negative correlation ($r > 0{\cdot}5$. $P < 0{\cdot}05$ in 8, $< 0{\cdot}01$ in 7) was found for older ages in 15 of 16 sets of independent data. The drug acetazolamide has been used to produce "artificial acclimatization", producing similar acid-base changes, and is reported (Evans) to have produced relief of intractable pain in terminal cancer patients. Some diseased states, such as achlorhydria and emphysema, in which there are chronic disturbances of acid-base relations, exhibit unexpected cancer rates.

Some other possible explanations of the apparent "altitude-effect", particularly that it is related to inefficiency of collection of data at high altitudes, seem implausible.

INTRODUCTION

SINCE IT IS thought that there are multiple causal factors in the many different types of cancer, significant correlations of the incidence of cancer in general, with any single environmental factor could hardly be expected, and very few have been found. The dominant correlation is, of course, with the age of the subject. The total age-specific incidence, including all types of cancer, rises almost exponentially, with comparatively very small rates below age 35 (as rates per 100,000 population of specific age groups, e.g. 30–35 years). There is also a significantly lower incidence, for the total of all types of cancer, for females than males above 50 years.

In research on growth and cellular division in tissue culture there is much evidence of the marked effect of changes in pH of the external medium. Eagle and his co-workers [1] have accumulated results on the rate of protein synthesis vs pH for a large number and variety of normal and tumour cells. The curves vs pH are usually triangular in shape with a sharp maximum of growth rate at a certain pH, characteristic of the particular cell line, falling off sharply for pH values on either side of the maximum. Sensitivity to changes of pH is such that 0·2 pH units is usually sufficient to reduce the growth rate to half the maximum value. Little is known of the corresponding changes in pH within the cell. If the cell is well provided with "buffers", it would likely be less than the 0·2 units of the external medium.

In the mammal, the pH of blood is of course

Accepted 12 December 1974.

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kept to relative constancy (by regulation of breathing and by the kidney). Nevertheless, there are some chronic conditions in which the intracellular pH may be abnormal. One of these is in the acclimatization to high altitude of men and other animals. The change is initiated as a response to hypoxia at high altitude, *i.e.*, hyperventilation results in excessive loss of carbon dioxide and a rise of blood pH. In about a week, the blood pH may return to normal. However, as long as the animal stays at high altitude, the alkali reserve of the body is markedly abnormal [2] so there is very probably a disturbance of acid–base relations within the cell. The receptor area for hypoxia response is, of course, the chemoreceptors of the carotid body, and Heath and his co-workers [3, 4] have shown, in animals and man residing at high altitudes, and in man at low altitudes suffering from disease accompanied by chronic hypoxemia, that there is a very marked increase in weight and size of the carotid body. Nature has thus provided an "experiment" in which we might see if chronic disturbances of acid-base balance affect the incidence of cancer. We have, therefore, examined the data available to us on rates of incidence of cancer in different parts of the world, looking for a correlation of age-specific rates with altitude. The data is, of course, disappointingly very small, compared to what we would wish, since results on the very large populations of Asia living at a variety of altitudes are not available, except in a very few scattered instances.

We knew of only two truly independent sources of statistical data of sufficient numbers of geographical sites and sufficient variation of altitude to be expected to show significant correlations.

The first source was the publication of the International Union Against Cancer (U.I.C.C.) on the incidence (registration) of cancer in five continents [5]. This gives figures for some 30 regions, varying from cities like Liverpool and Birmingham, England, to some provinces in Canada, to whole countries like Sweden, South Africa, or New Zealand. Very specific information is given about the criteria of registration, hospital facilities, demographic and geographic limits of the particular survey, with critical comments as to the adequacy of medical services and diagnosis. In some cases the validity of the data is questionable, for various reasons given in the text, but for the correlation analysis we included all regions listed (which would make it harder, rather than easier to obtain significant correlations). The tables give the rates per 100,000 population for 5-year age groups, for some 35 groups of different types of cancer according to the scheme of international classification, and the totals of all types of cancer, age-specific.

Our second major source of data was the report of W.H.O. on total deaths, rather than registration of cancer, in 36 different countries for the year 1965 [6]. Population of the regions is given in a separate set of tables, which allowed calculation of the rates per 100,000 population. Similar classifications and age-groups are given, but there is no critical assessment of reliability of the surveys, the data being accepted without question from official sources and governments. Ten of the regions coincide, at least in name, with those in the data on registration, and this gave an opportunity to compare the reported death rates with the reported "incidence". In these, the registration was always higher than the mortality rate, varying from 10 to 100 % greater. Fortunately, the mortality data include several new regions of altitude above 500 m. The regions surveyed vary from single cities to large countries, in which the population lives at a great variety of altitudes. We needed some sort of population-weighted "mean altitude", and this was done by a Mr. Edward Avey, who studied the distribution of populations between the larger cities and rural areas of a given country or region, with the known altitudes of the different regions. His estimates were, of course, "blind" *i.e.*, not influenced by knowledge of the cancer statistics. His weighted-mean values were accepted without change. In several countries considered to be of high altitude, his weighted-mean altitudes were lower than expected, because populations tend to live in the valleys rather than in the mountains. The range of mean altitudes calculated varied from sea level to 1780 m (Johannesburg). In all, the lists contained 13 regions with calculated population-mean altitudes over 500 m. (See Appendix).

A third possible source of data was the publication of the Department of Public Health, Tohoku University, Japan, on cancer mortality in 24 selected sites [7]. The data here might not be considered as independent of the W.H.O. data on mortality, except for differences in the years surveyed. Also, the list included only two regions of mean population altitude above 500 m, thus the regression with altitude could not be expected to be significant.

We made one further attempt to find the correlation, in data for the total death rates from cancer in the counties of California whose mean altitudes differ greatly. A plot of the

overall cancer rate vs altitude showed no regression at all and normal distribution of scatter at all altitudes. This is to be expected from the smallness of these geographic units and probable mobility of their populations. On the other hand, too large a geographic unit, including both high and low altitudes, is disadvantageous, since altitude effects will be less evident after the averaging. There is obviously an optimal size of unit for our purpose. The best possible data for our purpose would be, of course, from a large sub-continent like India, including age-specific rates for regions of high vs low altitude, collected by a single agency. This is not available to us.

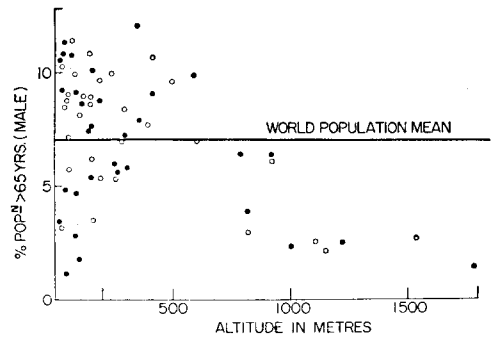

Fig. 1. Distribution of ages in the populations vs altitude. The percentage of the population above 65 years of age is taken as an index of population-age-distribution (P.A.D.). The data is shown by solid dots from U.I.C.C. [9], *that by open circles from W.H.O.* [10].

Evidence of an "altitude effect"

A purely preliminary exploration was made of the correlation of total rates (all age groups included) vs mean-population-altitude. There was very great scatter at the low altitudes, in which most of the data clusters, but a quite remarkable and significant negative regression (less cancer at higher altitudes) of total cancer rates with altitude evident from the scatter graphs (only above 500 m) in the two sources of data (U.I.C.C. and W.H.O.). The total cancer rate appeared to decrease on the average by about 100 cases per 100,000 population for each 1000 m of altitude. For the highest altitudes in the lists the rates were one-half to one-third those at low altitudes. The absence of any "altitude effect" at altitudes below 600 m would, of course, be consistent with the response to anoxia (acclimatization), which does not occur until there is a considerable "threshold" of anoxia. However, it was considered unjustifiable to calculate correlation coefficients and regression slopes which excluded the data at lower altitudes, though this would obviously yield higher values of correlation coefficients. In all the statistics, all of the very low altitudes were included.

However, since the age distribution of the populations might well be very different, with "younger" populations at higher altitudes, this apparent regression might well be due to this factor alone, and not a true altitude effect. This caution proved to be justified. From the data, an index of "population-age" was calculated as the percentage of the total population that was over 65 years of age. Figure 1 gives the result, as well as indicating the range of mean-altitudes available in our data. It is certainly true that for altitudes above 500 m the index of age distribution lies below the world average, and we must, therefore rely entirely on age-specific rates to establish an altitude effect, as other than indirect, due to differences in population-age-distribution.

It is obviously impossible to present all the data, for all age-specific groups (five-year intervals) in a concise form. We therefore arranged the lists of regions in order of their estimated population-mean altitudes, and took the six regions of highest vs the six of lowest altitude in the lists, calculating the mean cancer rates and SE of these means, for all of the age-specific groups. The results are presented in Figs. 2 and 3, which represent four independent sets of data. The rates for low vs high altitude are remarkably similar, and certainly not significantly different, up to age 60 or 65, but the differences become increasingly statistically significant (note lack of overlap of areas of mean ± 1 S.E.M.) at higher ages.

This technique of comparing six at the top with six at the bottom of the order of altitudes was useful, in showing that any correlation

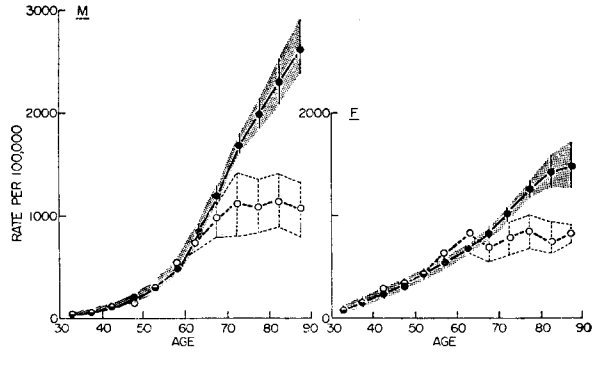

Fig. 2. Age-specific rates of "incidence" of cancer vs age for the six places of highest vs the six places of lowest altitude (U.I.C.C. data). The SE of the means are shown by the vertical bars. Note the significant differences at ages above 65.

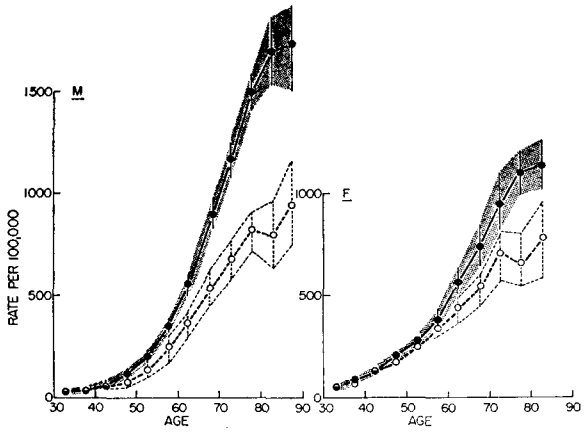

Fig. 3. *As in Fig.* 2, *but for W.H.O. data on death rates.*

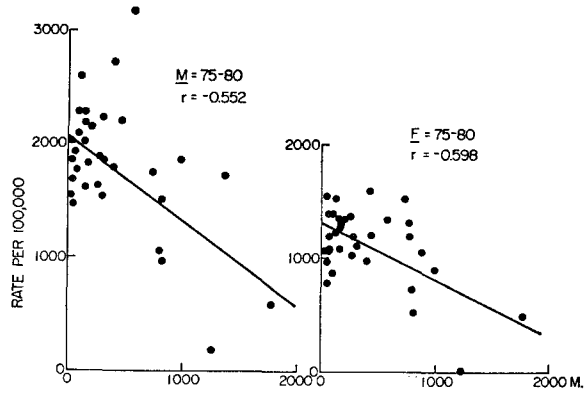

Fig. 4. *Illustrating one of the negative correlations of Table* 1 (*columns* 3 *and* 7) *of age-specific rates with altitude. The straight line is the calculated regression, including all the points, and the correlation coefficient is significant to the* 99% *confidence level.*

with altitude was confined to the older ages, but, of course, it is inefficient in that it utilized less than half of the data, as it omitted the data for all the intermediate altitudes. Accordingly, the regression lines and coefficients of correlation were computed for age groups 65–70, 70–75, 75–80, and over 80 in the four sets of data. The results are shown in Table 1. Of the 16 independent correlations, eight were significant at the 99% level of confidence, seven at the 95% level, and only one at a lower level. However "unreliable" the data may be considered to be, the chance that without some factor associating cancer with altitude in the data, such a set of apparent correlation coefficients would turn up is very small indeed, to the verge of impossibility. Most of the correlation coefficients for males exceeded 0·5, which would mean that more than 25% of the variance in cancer rates, for these ages, was associated with the altitude (75% with the many other random factors affecting cancer rates). This is remarkable for any one factor in cancer statistics, and distribution of age in the populations could play only a very small role indeed in these groups with narrow ranges of age. Figure 4 gives a typical example of one of these regressions for a specific age group. Analysis of age-specific data down to ages 50–55 still shows some significant correlations with altitude, but at lower ages there is very little indication of any reduction of cancer rates except in the regions of very high altitude.

Dependence of altitude effect on types of cancer

The data used gives the age-specific and total rates for some 40 different types of cancer, according to an international classification. We used the device of calculating the percentage of all cancers for a given region that were in a given group of types of tumours (reduced from 40 to 10 broad categories), to give a "profile" (histogram) of types of cancer. This was done for the six places of highest vs the six of lowest altitude in the U.I.C.C. data. The profiles were remarkably similar and there was no indication of a significant difference between

Table 1. *Statistical evaluation of correlations of age-specific rates*/100,000 *with altitude*

Statistic	Age	Incidence rates U.I.C.C. 65–	70–	75–	> 80	Death rates W.H.O. 65–	70–	75–	> 80
Coefficient of correlation r*	M	−0·508	−0·499	−0·552	(−0·214)	−0·608	−0·590	−0·580	−0·613
	F	−0·291	−0·410	−0·598	−0·352	−0·291	−0·398	−0·344	−0·334
Intercept A†	M	1306	1688	2107	2270	1023	1342	1638	2006
	F	830	1034	1306	1408	560	757	999	1288
Standard error of estimate	M	±255	±391	±470	±771	±180	±274	±330	±483
	F	±167	±218	±274	±414	± 83	±140	±187	±310
Regression Slope B*	M	−0·376	−0·562	−0·767	−0·406	−0·376	−0·562	−0·767	−0·406
	F	−0·127	−0·244	0·505	−0·375	−0·127	−0·244	−0·505	−0·375

*Where underlined, the confidence in r is > 99%, where not underlined > 95%, and where in brackets < 95%.
†A and B in the regression equation. Rate/100,000 = A+B (Altitude in m).

the means for any category. For example, the greatest percentage of all cancer was for the "gastrointestinal tract", and the mean percentages were $25{\cdot}5 \pm 4{\cdot}9$ S.E.M. for the six high altitude, cf. $24{\cdot}7 \pm 2{\cdot}2$ S.E.M. for the six low altitude regions. The next highest percentage was for lungs and thorax, $11{\cdot}6 \pm 2{\cdot}0$ vs $9{\cdot}7 \pm 1{\cdot}5$. The "altitude effect", whatever its cause, is apparently a non-specific reduction in reports of cancers of all types.

Other correlations, cancer and altitude

We know of one other report of a strong negative correlation of cancer with altitude. This is in the case of Burkitt's lymphoma, which is confined to a region of Central Africa, and to children. Burkitt [8] states "Altitude seems to be the determining factor.... The only district in Uganda from which we have recorded no single case is the very densely populated southwest, which is mountainous country at an altitude of 5000 feet (1500 m)." Since the annual rainfall is much less than average in this region, the correlation might be attributed to many other vectors than altitude *per se*, e.g., distribution of an insect vector.

Medical missionaries penetrating to remote regions very often have reported an absence of cancer cases, but as "civilization" advanced into these regions, the cancer rates usually were found not to be unusual [9]. The State of Hunza, with a population over 20,000 seems to be an exception, since over 60 years of reports by Medical residents have failed to find a single case (according to Stefansson) whereas one would expect at least 20 cancer deaths per year, from the mean values for low altitude elsewhere. Hunza is in the Himalayas, with no part of the State below 15,000 feet (4600 m).*

Simulated acclimatization to altitude, acetazolamide (Diamox)

Acclimatization to altitude takes a week or more, and rapid transport to high altitude can produce "altitude sickness". Pre-treatment with several drugs has been tried to alleviate this and to produce the acclimatized state sooner. Acetazolamide (Diamox) is one of the most successful. It is an anti-carbonic anhydrase, and produces changes in acid-base relations (reduction in alkali reserve) similar to those in acclimatization to altitude [10]. We therefore looked for evidence in the literature that this drug had effects on cell division and on cancer. Evans [11] used it, on the theory that pain-sensitivity was affected by acid–base relations, on a large group of patients with intractable pain, nearly all of whom happen to be "terminal cancer patients". He verified the changes in acid–base produced by the drug, and there was evidence of considerable relief of pain. The relief might, of course, not only be due to an effect on pain-sensitivity, but also on a decrease in rate of growth of the tumours. Many of the patients on the drug in the test period continued its use, and some have survived many years more than expected, though this cannot be reliably related to the drug alone because radiation and chemotherapy was given in addition. (Personal communication by Dr. Evans).

In large doses acetazolamide is known to be "embryocidal", and there is a report in the clinical literature [12], of a 73-year old man who died from a suppression of cells of all types in the bone marrow after taking 250 mg/day of Diamox.

DISCUSSION

The fact of the strong and statistically significant negative correlation of cancer with altitude in the data used, for the age groups above 60 years, must be accepted, but of course, the interpretation of this fact in terms of causal relations will be highly controversial. The suggestion most often made by colleagues to whom the correlation has been pointed out, is that it results from inefficiency of cancer surveys at high altitude compared to lower altitudes. Communications, medical services, and cancer registration of the populations are, of course, likely to be less well developed at high altitudes. However, there are three reasons why this explanation does not seem plausible: (1) for the very high altitude regions the degree of inefficiency would have to be such that half the cases (e.g. cancer deaths) or more were missed; (2) the list of high altitude regions, while it includes some underdeveloped regions, also includes places where medical care is relatively sophisticated, as in Johannesburg, Colombia, Venezuela, Mexico, or Alberta, Canada; (3) advocates of inefficiency of surveys at altitudes as the explanation, would have to advance a reason why at ages below 60 the surveys were apparently efficient, but became inefficient for the older people. (Figs. 2 and 3).

*While this paper was in press, a paper appeared showing a remarkable negative correlation of death by leukemia in the United States with altitude. Over 500 geographical locations were used and segregated into altitude increments of 400 ft [ECKHOFF *et al. Health Physics* **27,** 377 (1974)].

We also might be asked to explain why the "altitude effect" is seen only for the advanced ages. The small proportion of cancers detected at young ages are usually rapidly growing malignant forms, while the majority of all cancers are, perhaps, very slow growing tumours, which might take as long as 30 years of "incubation" before they are clinically detected or lethal.

Another very reasonable suggestion is that there may be a "selection effect" on the part of the older people in the population, In that the "weaker and more diseased" elderly people might not be able to cope with the rigours of high altitude life and may tend to reside at lower altitudes. Here then is an assumption that cancer in general attacks the "weaker and more diseased", more than it attacks the strong and otherwise healthy. This assumption may not be generally acceptable. If the selection were specific rather then general, *i.e.* those who cannot cope with life at high altitude do not live there, this explanation of the correlation is similar to ours. We know that successful coping with long-term residence at high altitude depends on the physiological changes in acclimatization to altitude, involving acid-base readjustments. The suggestion of a "selection factor" in the population leads therefore, to the same explanation, namely that acclimatization to altitude may involve resistance to cancer.

If it is suggested that the correlation is related causally to some other environmental factor closely associated with altitude, there would be, of course, a wide choice other than the acid-base change in acclimatization to altitude. One might postulate the absence of some toxic atmospheric factor, or an insect vector, or some physical factor like humidity or temperature that might be well correlated with altitude. The existence of the correlation with altitude merely is consistent with our theory that acid-base changes in acclimatization to altitude might be responsible. "Circumstantial" evidence from conditions where disturbed acid-base relations exist, other than related to acclimatization to altitude, is required to strengthen the case. The very strong evidence in tissue culture has already been discussed in the Introduction.

There are only a few diseases where marked changes in pH persist for long periods (e.g. the acidosis of diabetes is removed by insulin therapy). The best example is achlorhydria, which accompanies pernicious anaemia. Treatment of the anaemia does not remove the chlorhydria. The stomach cells of the patient continue not to secrete the strong acid of the corresponding normal stomach cells, so these cells must be supposed to have abnormal acid-base conditions. It is encouraging to our hypothesis to note that the report of a Research Committee of W.H.O. on a conference on cancer of the gastrointestinal tract [13] states—"The rate of gastric cancer in pernicious anaemia patients has greatly exceeded expectations many times, as have rates for achlorhydria; from four to five times the expected number of gastric cancers are found in achlorhydric patients".

Chronic emphysema is another example, for the cells of the lungs are exposed to unusual concentrations of carbon dioxide and are likely to be abnormally acid. The incidence of cancer of the lung is, of course, very high indeed in this disease. Since most of the patients are heavy smokers of cigarettes, the increased incidence is usually attributed to this, but it might well be mediated by an acid-base disturbance.

What is needed is "prospective" rather than "retrospective" research at the clinical investigative level on the effect of manipulations of acid-base relations, by drugs like acetazolamide, or even ammonium chloride, which are used freely, in the case of acetazolamide as a mild diuretic on all kinds of patients. Investigations should be on patients with forms of cancer where quantitative measurement of the effect, if any, can be made from day to day (e.g. in leukemia). One would think that merely on the basis of the impressive work of Eagle [1] on tissue culture, such clinical investigation would be indicated. The suggestive additional evidence cited in this article should give a further stimulus to research on how changes in pH may underlie the control of cellular division in health, and be used in controlling neoplastic disease.

We undertook this investigation because of our pursuit of a speculative, very general theory of how the exchange between cells of a "key substance" or substances, whose concentration intrinsically cycles in each cell, could control cellular division ("contact inhibition") [14]. We had already suggested that H^+ or OH^- ions would be excellent candidates for such "key substances" [15]. Recent evidence on fibroblast proliferation [16] suggested that the effect of pH of the external medium is greatest in the confluent stage of culture, *i.e.*, on intercellular reactions and "contact inhibition". The finding of these remarkable and significant correlations of cancer with altitude in the data available supports that suggestion.

Acknowledgements—Without the excellent work of Mr. Edward Avey in estimating the mean altitude for the populations surveyed, the correlation with altitude would not have been reliably established. Dr. Peter Canham, of this department, did much of the computing of regression and correlations, in which also Mr. Peter Higgins, graduate student in Biophysics, assisted. I am greatly indebted to Dr. K. Stavraky, of the Department of Epidemiology, for finding the sources of data for me, and to Dr. Wanklin and Professor Carol Buck of the same department, for helpful suggestions.

APPENDIX

List of regions in C.I.C.C. and in W.H.O. data with their estimated population-weighted mean altitude.

The regions are arranged in descending order of altitude (given in metres).

C.I.C.C. (Incidence of cancer)

Johannesburgh, S. Africa, 1780; Uganda, 1214; Cali, Colombia, 1000; Yugoslavia, 910; Chile, 810; Alberta, Canada, 760; Saskatchewan, Canada, 580; Manitoba, Canada, 410; Iceland, 300; Newfoundland, Canada, 300; Israel, 255; Jamaica, 250; New York State, U.S.A., 195; Puerto Rico, 156; Finland, 150; Norway, 150; New Zealand, 140; Connecticut, U.S.A., 105; New Brunswick, Canada, 100; Birmingham, England, 100; Liverpool, England, 80; Hawaii, 80; Sweden, 60; Japan, 32; London, England, S.W. Region, 30; London, England, S. Metro, 30; Denmark, 26; Hamburg, Germany, 25; Netherlands, 10.

W.H.O. (Death rates from cancer)

Mexico, 1540; Venezuela, 1150; Mauritius, 1100; Colombia, 1100; Yugoslavia, 910; Chile, 810; Spain, 600; Switzerland, 500; Austria, 420; Czechoslovakia, 395; U.S.A., 295; Canada, 290; Israel, 255; German Fed. Rep., 234; Portugal, 233; Poland, 180; France, 180; Ceylon, 160; Finland, 150; Norway, 150; Italy, 140; New Zealand, 140; Hungary, 120; Greece, 100; S. Ireland, 90; Belgium, 88; U.K. England, Wales, 60; Japan, 60; Sweden, 60; Australia, 60; Scotland, 50; W. Berlin, 50; N. Ireland, 32; United Arab Republic, 26; Denmark, 26; Netherlands, 10.

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