Biometeorological Survey

Volume 1 1973 - 1978

Part A Human Biometeorology

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Part A

BIOMETEOROLOGICAL SURVEY
VOLUME 1 1973-1978

Part A Human Biometeorology

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Introduction

The impact of the weather and climate on the living organism has been studied intensively during the last thirty years. It is a topic of particular significance for the developing countries, while providing medical and other researchers with a wealth of vital information. The compilation of the present work was undertaken to present a detailed overview of the research carried out since 1973, the last year to be dealt with in previous dedicated review volumes. The period 1945–1963 was covered by the book *Medical Biometeorology* (Elsevier Publ. Co., Amsterdam) which summarizes the major findings of 4400 biometeorological publications.

From 1963 to 1973 the number of new biometeorological publications exceeded 10 000 titles, 7100 dealing with human biometeorology and 2900 with animal biometeorology. These were reviewed in the series *Progress in Biometeorology* (Swets & Zietlinger Publ. Co., Lisse), which consists of seven books: four on human biometeorology, two on animal biometeorology and one on plant biometeorology.

The present two-part volume gives an overview of the period 1973–1978. Part A presents 27 research reviews on the effects of weather and climate on humans, while Part B contains 16 papers on the effects on animals. Emphasis is also on extensive lists of references, classified by subject, and we have tried to provide the research worker with a comprehensive guide to assist him in seeking new biometeorological results and techniques. This recent survey of human and animal biometeorology has been prepared not only for physicians and veterinarians, but also for biologists, meteorologists, engineers, sociologists and clinical psychologists who are involved in the study of the effects of the physical environment on human populations.

Leiden
September 1979

S.W. Tromp
J.J. Bouma

Thermal Effects, Human Comfort, Architecture

Thermoreception and Comfort in Man

H. Hensel, *University of Marburg, FR Germany*

Thermoreception is involved in temperature sensation, in thermal comfort and in thermoregulation of the body (Hensel, 1973a). The term 'thermoreception' is now widely adopted; according to the Encyclopaedia Britannica (Hensel, 1974a), thermoreception is 'a process in which different levels of heat energy (temperatures) are detected by living things'.

The possible neural processes involved in temperature sensation, thermal comfort and temperature regulation are summarized in the schematic diagram in Fig. 1. We can assume that the signals for comfort and discomfort originate from thermosensitive structures in the central

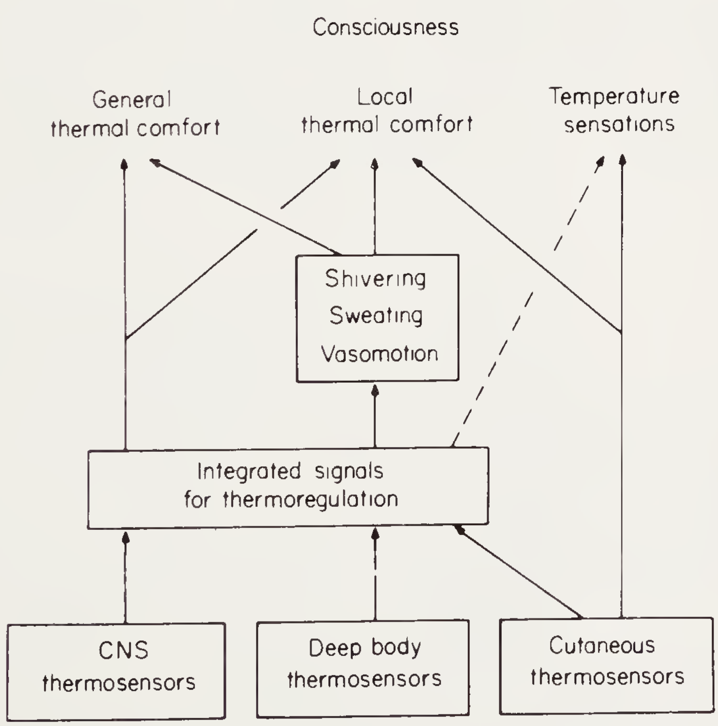

Fig. 1. Neural processes in thermal sensation, comfort and temperature regulation

nervous system, other deep body thermosensors, cutaneous thermoreceptors, and structures involved in shivering, sweating and vasomotion. The integrated signals from various internal and external thermosensors give rise to general thermal comfort but are also involved in local comfort. The same holds for the processes of thermoregulation. As to the thermoreceptors in the skin, they contribute on the one hand to the integrated signals for thermoregulation and thermal comfort but on the other hand their signals are mediated through separate pathways involved in temperature sensation. The local cold sensations are practically independent of the subject's general thermal state, whereas a slight influence may be assumed for the warm sensation (dashed line on the diagram).

Under the conditions of daily life, we do not clearly distinguish between thermal comfort and temperature sensation. A closer investigation, however, reveals that both kinds of experience can be separated psychologically and physiologically. Temperature sensations can be described as being directed towards an objective world, while thermal comfort refers to the subjective state of the observer. The verbal scales describing temperature sensations are based on the terms 'cold' and 'warm', whereas thermal comfort and discomfort can be characterized by the terms 'pleasant' and 'unpleasant'.

In human subjects, specific cold and warm receptors have been established by recording single fibre activity from cutaneous nerves (Hensel, 1973b, 1974b, 1976; Konietzny and Hensel, 1975, 1977). At constant skin temperatures, cold and warm receptors are either silent or show a static activity whose maximum frequency is in the range between 10–36 °C for cold fibres and between 41–47 °C for warm fibres (Fig. 2). On dynamic cooling, cold receptors respond with an overshoot in frequency, followed by an adaptation to a new static level, while dynamic warming leads to an undershoot and adaptation to a new level. Warm receptors respond in the opposite way, namely, with an overshoot on dynamic warming and an undershoot on cooling. Figure 3 shows the static and dynamic discharge of a single warm fibre recorded by a microelectrode from the superficial branch of the radial nerve in a human subject. The static frequency increases with constant skin temperature up to 45 °C. Warming the skin with linear temperature rates from +0.5 to +1.5 °C/s caused a transient overshoot in the frequency of the discharge with peak frequencies depending on the rate of temperature change (dT/dt).

In the tongue of cats and the skin of monkeys practically all cutaneous cold receptors exhibit a grouped or burst discharge at certain constant temperatures (Hensel, 1973b, 1974b; Iggo and Young, 1975; Dykes, 1975; Bade, Braun and Hensel 1977). This burst discharge shows a monotonic change of certain parameters with temperature

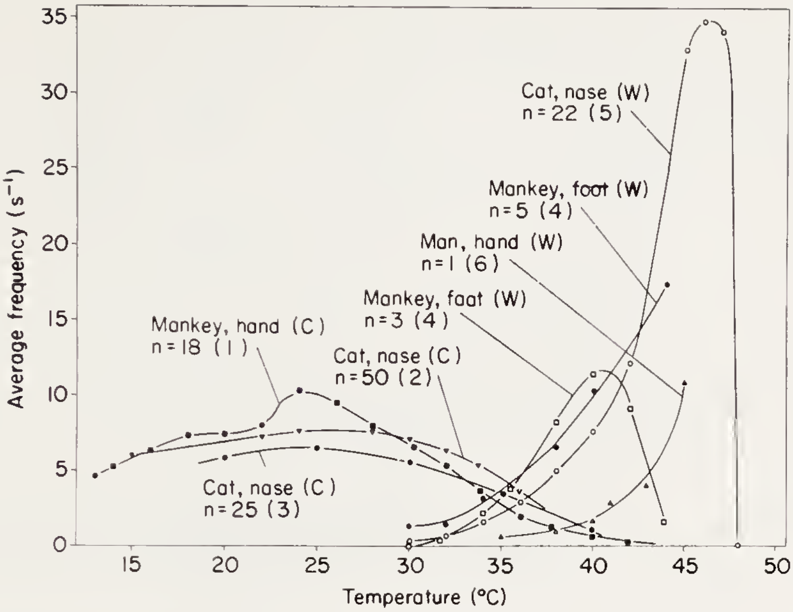

Fig. 2. Static single fibre activity of cold (c) and warm (w) receptors

(1) Dykes (1975); (2) Hensel (unpublished); (3) Kenshalo *et al.* (1971); (4) Hensel (1973); (5) Hensel and Kenshalo (1969); (4) Konietzny and Hensel (1975)

even in the range where the average frequency follows a bell-shaped function (cf. Fig. 4). For example, the number of spikes per burst as well as the time interval between the bursts increase with decreasing static temperature. However, most of the cold fibres in humans exhibit no static bursting. The only exception so far was one few-fibre preparation but even here pronounced bursting occurred only during the dynamic state of cooling (Hensel, 1976).

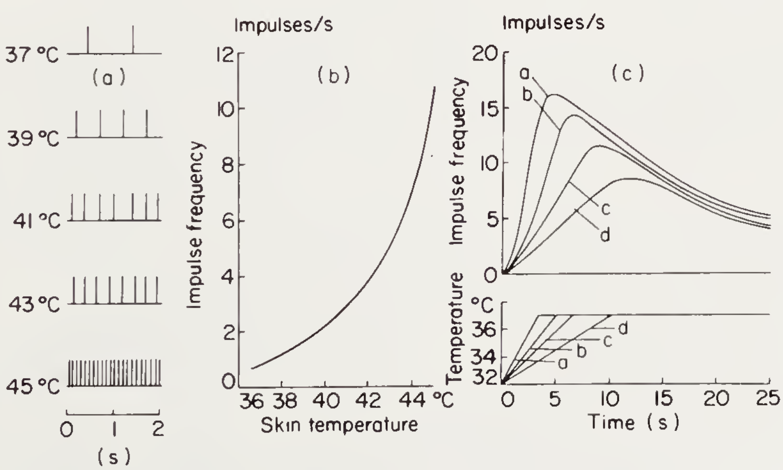

Fig. 3. Static and dynamic discharge of a single warm fibre from the superficial branch of the radial nerve in a human subject

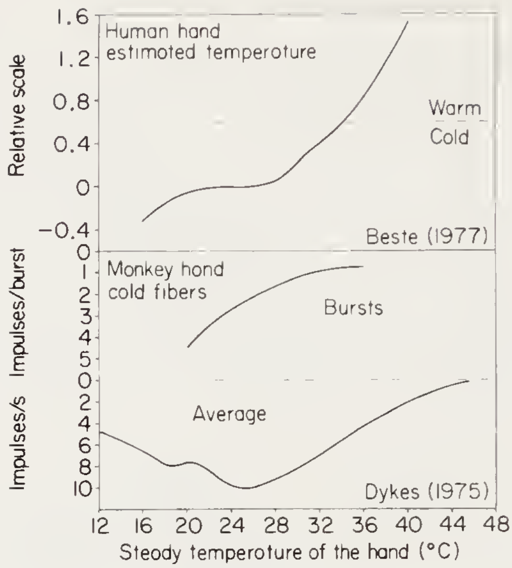

Fig. 4. Comparison between static temperature sensation in man and static cold fibre discharge in monkey

It is well established now that warm and cold sensations are mediated by a dual system of specific warm and cold fibres. This is further supported by the fact that warm or cold sensations can be selectively blocked by local anaesthetics (Fruhstorfer *et al.*, 1974).

When small areas of stimulation and small temperature changes are used, cold or warm receptors may be excited without conscious sensations. The latter are only observed when a certain number of impulses per unit of time reaches the central nervous system. Attempts have been made to determine this 'central threshold' for single cold and warm spots in human subjects. The threshold of cold sensation would correspond to about 80 impulses and that of warm sensation to about 9 impulses/s (Järvilehto, 1973; Konietzny *et al.*, 1977).

In contrast to numerous studies with dynamic thermal stimulation, thorough investigations of human temperature sensations have only recently been performed (Hensel and Beste, 1977; Beste 1977). Figure 4 shows the estimated static temperatures of the human hand as a function of the static physical temperature. As can be seen, the course of static temperature sensation does neither correlate with the average discharge frequency of cold receptors in the monkey's hand nor with the parameters of the burst discharge. In addition, there is no evidence that the burst parameters will be transferred through higher synapses of the thermosenstitive pathway in the medulla and thalamus of the monkey (Poulos, 1975) or the spinal cord of cat and monkey (Burton, 1975). The static response profiles of single central neurons remained similar to the bell-shaped curve of mean frequency observed in the periphery.

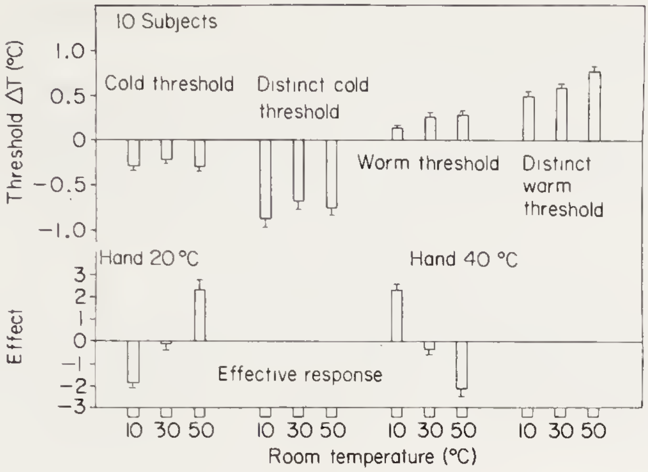

Fig. 5. Thermal thresholds and effective response to thermal stimulation of the hand at various room temperatures

This brings up the question whether the discrimination of constant temperatures, particularly in the cold range, might have its neurophysiological correlate in a simultaneous pattern of units with different properties. An analysis of static activity curves from cold fibres in the cat's infraorbital nerve revealed a rather inhomogenous distribution over the temperature range, the static maxima being accumulated at certain temperatures (Hensel, 1976). These findings may give some support for the hypothesis that at lower constant temperatures receptor populations with different properties may be activated.

Under certain conditions marked dissociations between temperature sensation and thermal affects may occur. For example, warm stimuli applied to the hand of hypothermic subjects were pleasant, and cold stimuli were unpleasant, whereas the opposite was true when the subjects were hyperthermic (Cabanac, 1972). In contrast to thermal comfort, the cold stimuli applied to the hand always evoked a cold sensation and the warm stimuli a warm sensation. From these facts we must conclude that thermal comfort does not reflect the activity of peripheral thermoreceptors alone but rather an integrated state of the thermoregulatory system.

Whether the general state of thermoregulation may also modify the local cold and warm thresholds was tested in subjects exposed to room temperatures of 10, 30 and 50 °C, respectively (Hensel, 1977). At 10 °C ambient temperature the average skin temperature was 27.3 °C and the rectal temperature 36.5 °C, while at 50 °C ambient temperature the respective values were 36.8 °C and 37.5 °C. The arm was thermally insulated from the ambient conditions, the hand being placed on a large thermode. Linear thermal stimuli of + 1.5 °C/min and − 1.5 °C/min were applied. In addition, the other hand was immersed alternately in stirred water baths of 20 and 40 °C, thereby judging the degree of pleasantness on a subjective scale.

Local cold thresholds on the hand are not considerably altered by ambients of 10 and 50 °C, whereas the pleasantness of cold stimuli of 20 and 40 °C is drastically modified by various room temperatures (Fig. 5). In contrast to the constant cold thresholds, the warm thresholds increase to a certain extent with increasing room temperature. This may be interpreted as a kind of 'masking' of the warm thresholds by the thermal afferents from the whole body. These findings indicate that the sensory channels for cold and for warmth may have somewhat different properties. Mower (1976) has also shown that the perceived intensity of peripheral thermal stimuli is independent of internal body temperature.

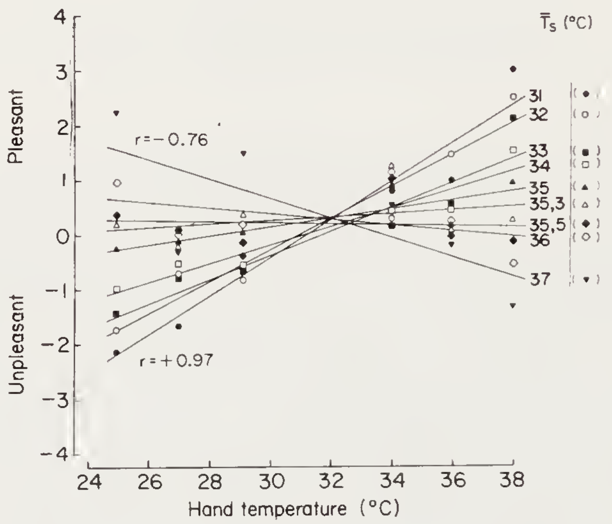

Fig. 6. Pleasantness of constant temperature of the hand between 25 °C and 38 °C at average skin temperature between 31 and 37 °C

The pleasantness of dynamic warm stimuli applied to the forehead is modified by the mean skin temperature, even when the internal body temperature remains unchanged (Marks and Gonzalez, 1974). This holds also for the pleasantness of static thermal stimuli applied to the hand. When the palm is kept at 25 °C and the room temperature slowly changed as to shift the mean skin temperature from 31 to 37 °C, the thermal effect elicited from the hand changes from unpleasant to pleasant. Since the rectal temperature remains practically constant, this effective change must be ascribed to cutaneous thermal effects alone. With constant hand temperatures of 38 °C, the thermal effect changes from pleasant to unpleasant during a shift in average skin temperature from 31 to 37 °C. The diagram in Fig. 6 shows the pleasantness of constant temperatures of the hand between 25 and 38 °C and average skin temperatures between 31–37 °C.

It is remarkable that in the neutral range of average skin temperature any constant temperature of the hand between 25 and 38 °C is rated neither pleasant nor unpleasant (neutral = 0), whereas distinct pleasantness or unpleasantness is observed only when the average skin temperature deviates considerably from the thermally neutral range. These findings agree in part with observations by Mower (1976).

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Studies on the Effects of the Physical Environment on Human Comfort

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INTRODUCTION

Since 1970 many new studies have been published on the effects of the physical environment on human comfort. Excellent review papers were written by Fanger, Olesen, Wyon and others in Scandinavia, by McIntyre and colleagues in the UK, by Givoni in Israel and by many other environmental experts in the USA (Hardy, Gagge, Yaglou and others) (for P.O. Fanger and B. Givoni cf. S.W. Tromp, 1974; Fanger, 1973c; Auliciems, 1971).

Due to urgent obligations of the mentioned experts the author was obliged to prepare this review paper based on the publications of Fanger, McIntyre, Olesen and Wyon. Their major publications have been summarized in the reference list attached to this paper.

DEFINITION OF THERMAL COMFORT IN HUMANS

Thermal comfort has been defined by the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE Standard, 55–66, New York, 1966) as 'that condition of mind which expresses satisfaction with the thermal environment'. At least 9 environmental factors influence the condition of thermal comfort: (i) air temperature, (ii) mean radiant temperature, (iii) relative air velocity, (iv) vapour pressure in ambient air, (v) internal heat production in the body determined by muscular activity, thyroid activity and other metabolic processes such as food consumption, etc., (vi) thermal resistance of clothing, (vii) thermoregulatory efficiency of the body, (viii) sex and (ix) psychological stress. Each of these nine factors were fully discussed in S.W. Tromp (1974).

Due to increasing urbanization and industrialization most people spend the greater part of the day indoors. Therefore, in recent years, the study of the effect of these nine parameters on thermal comfort and human efficiency, in the microclimate of the indoor environment, is rapidly developing.

HEAT BALANCE OF HUMANS

The principal condition required for thermal comfort in a given environment is the existence of a heat balance. Depending on the rate of thermoregulation efficiency of the subject, this balance can be reached more or less easily. Fanger (1970c) developed a heat balance equation in order to predict the required comfort conditions of a certain environment:

$$f\left(\frac{H}{A_{Du}}, I_{cl}, t_a, t_{mrt}, P_a, V, t_s, \frac{E_{sw}}{A_{Du}}\right) = 0, \tag{1}$$

where H/A_{Du} = internal heat production per unit body surface area (A_{Du} = DuBois area); I_{cl} = thermal resistance of the clothing: t_a = air temperature: t_{mrt} = mean radiant temperature; P_a = pressure of water vapour in ambient air; V = relative air velocity; t_s = mean skin temperature; E_{sw}/A_{Du} = heat loss per unit body surface area by evaporation of sweat secretion.

For a given activity level, the skin temperature, t_s, and the sweat secretion E_{sw}, are seen to be the only physiological variables influencing the heat balance in eqn (1). The sensation of thermal comfort has been related to the magnitude of these two variables. Experiments involving a group of subjects at different activity levels have been performed to determine mean values of skin temperature and sweat secretion, as functions of the activity level, for persons in thermal comfort. The results have the following form:

$$t_s = f\left(\frac{H}{A_{Du}}\right) \tag{2}$$

$$E_{sw} = A_{Du} f\left(\frac{H}{A_{Du}}\right) \tag{3}$$

Equations (2) and (3) are presented as the second and third basic conditions for thermal comfort. By substituting conditions (2) and (3) in (1), the desired comfort equation takes the following form:

$$f\left(\frac{H}{A_{Du}}, I_{cl}, t_a, t_{mrt}, P_a, V\right) = 0 \tag{4}$$

Using eqn (4) it is possible, according to Fanger, to calculate for any activity level (H/A_{Du}) and any clothing (I_{cl}), all combinations of air temperature (t_a), mean radiant temperature (t_{mrt}), air humidity (P_a) and relative air velocity (V) for the condition of optimal thermal comfort.

EXTERNAL FACTORS AFFECTING THE COMFORT OF HUMANS

Olesen and Fanger (1973) pointed out that the mean skin temperature and the temperature distributions over the human body are important for man's thermal sensation.

When a subject is in comfort in light clothing the highest skin temperatures are found on the head, the upper part of the trunk, and the abdomen; the lowest temperatures are found on the legs. The differences in temperature are moderate. The temperature distribution over the skin is significantly more non-uniform for females than for males ($p < 0.01$).

Men and women do not prefer a significantly different ambient temperature or a different mean skin temperature. By comparing the local skin temperatures of the two sexes, in general no great differences were found for 13 locations. Only on the feet (instep) was a significant difference found: females in comfort had a 2.1 °C lower foot temperature than males ($p < 0.05$).

The mean preferred ambient temperature was found to be 25.5 °C; this is in good agreement with the comfort equation which predicts that 25.6 °C will provide optimal comfort under the actual experimental conditions (used by Fanger *et al.*, 1973). The corresponding mean skin temperature (33.5 °C) is in good agreement with earlier investigations by Gagge *et al.* (1938), Hardy (1954), Yaglou (1941) and others. As the internal body temperature varies over 24 h it is conceivable that the ambient temperature preferred by humans varies during the day also. Fanger *et al.* (1973; 1974b) pointed out that the study of this phenomenon is of direct practical interest. Fanger's studies revealed that the preferred ambient temperature varied only slightly during the day, and that none of the fluctuations deviated significantly from the mean value of 24.5 °C. There was, however, a tendency for the ambient temperature to increase slightly during the morning, while, surprisingly, constant temperatures were preferred in the afternoon. The preferred mean temperature was the same in the morning and in the afternoon. No difference was observed between the preferred ambient temperature of males and females.

As expected the rectal temperature increased slightly during the day as did the skin temperature. However, this slight increase in skin temperature did not cause the subjects to prefer an ambient temperature during the afternoon different from that of morning.

Summarizing, it can be stated that thermal comfort conditions for humans seem to be constant throughout the day. In spaces occupied by people performing sedentary work Fanger recommended that the ambient temperature be kept at the same level during the entire working day.

Fanger (1973h) also studied the variability of the ambient temperature preferred by humans from day to day. It was found that this variability is remarkably small. This indicates that man is quite consistent from day to day in his thermal preference.

The mean preferred temperature for sixteen subjects was 25.3 °C. This may appear to be unusually high, it should be remembered, however, that the clothing in Fanger's study was relatively light (0.6 clo*). The observed preferred temperature is in reasonable agreement with the comfort equation of Fanger, which for the actual experimental conditions predicts that a temperature of 25.6 °C will provide optimal comfort.

No significant difference was observed between males and females in their ambient temperatures or in the 'day to day' standard deviation. The ambient temperature preferred by humans shows only minor variations from day to day (assuming the same clothing, activity, air velocity and humidity). The standard deviation was found to be 0.6 °C for seated subjects clothed in 0.6 clo.

In 1977 Fanger studied the preferred room temperatures for 16 winter swimmers who had been exposed to cold shock daily by bathing in the sea (0–6 °C) during at least two winter seasons. The results showed no significant differences between the ambient temperatures preferred by a control group which lived under normal conditions.

McIntyre (1977) studied the influence of overhead radiation on human comfort. Several radiant heating systems are used in offices and factories as overhead downward facing heat emitters. Overhead radiant heating produces a thermal environment which is asymmetric. Experiments have shown that a vector radiant temperature of more than 10 K in an occupied space causes discomfort in the people working in this space and produces complaints.

McIntyre and Griffiths (1975a) also studied reports claiming that people performing difficult intellectual tasks would require lower temperatures than when unoccupied. Since many buildings are designed to accomodate purely intellectual workers a scientific study of the problem was proposed in the Electricity Council Research Centre at Capenhurst, Chester, England. 24 students of both sexes in the age of

*'Clo' is a unit of thermal insulation, being the amount provided by man's normal everyday clothing; 1 clo represents 1/4 in thickness of wool.

16–20 years were used. An analysis of the subjective findings did not show any difference between periods of intellectual and recreational activity. The authors concluded that mental effort has no effect on subjective assessments of warmth.

As pointed out in the last part of this paper these experiments of McIntyre and many studies by Fanger are not, in our opinion, conclusive. Mental efforts of youngsters are entirely different from older adults. For example a high noise level is experienced as a pleasant distraction by young people in our present very noisy environment whereas it distracts and hampers many physiological functions in older subjects. In our opinion similar experiments can only be conclusive if carried out with very large groups of subjects of different age groups.

DESIGN OF BUILDINGS IN THE TROPICS

Studies were carried out by Fanger (1972b) on the possibilities of improving thermal comfort of man in the tropics. For this purpose Fanger compared the reactions of inhabitants of Denmark with those of subjects who, having lived their entire life in the tropics, were tested 48 h after their arrival in Copenhagen. The Danish subjects lived 10 days in an environmental chamber at 35 °C and 50% relative humidity. Each day the subject cycled on an ergometer in the chamber for 2 h. No significant change in the preferred ambient temperature was found although the subjects were acclimated during 10 days to a very warm environment. There was also no change in the comfort values of skin temperature and evaporative heat loss. The same test was carried out with the subjects which just arrived from the tropics. It was found that they preferred a mean temperature of 26.2 °C against 25.4–25.7 in the Danish subjects. During periods of comfort there was no significant difference either between mean skin temperatures or between evaporative weight losses.

A better design of buildings in the tropics could increase enormously the level of human comfort. In the design of buildings certain principles should be followed in order to satisfy the comfort conditions or at least decrease the heat stress to which people are exposed in the tropics.

According to Fanger the main thermal principles to be followed in order to obtain a confortable indoor climate in the tropics are the following:

General principles: light colours of roof and exterior walls; insulation of roof and walls; the long axis of the house lying east/west; screening of windows from the sun, and no windows on east and west sides.
In hot-dry climates: house closeable during day: through-ventilation during night, and high heat capacity of roof and walls.
In warm-wet climates: through-ventilation during day and night

and suitable orientation of the house in relation to the prevailing wind.

It must be ensured that the roof is painted white or at least a light colour, so that the main part of the strong solar radiation is reflected. If the roof is dark, large quantities of heat are absorbed and transferred into the house, hence the mean radiant temperature indoors increases. Furthermore, a certain amount of insulation will be necessary, especially of the roof, but preferably also the walls; again, this is to prevent the absorbed solar radiation from penetrating into the house. Preferably, the house should be placed so that its long axis lies east/west. With the high altitude of the sun at midday, a minimum of sunshine penetrates through the windows. Suitable screening of the windows is often necessary, for instance, by an overhanging roof, and in order to avoid the sun shining in when it is at low altitudes in the morning and in the evening, no windows should be placed east/west.

Apart from these principles for building design in the tropics, more specific factors must be considered in hot-dry climates. The main characteristic of this climate is the large diurnal temperature changes, hot days and cool nights with a temperature difference of 25 °C or more. The principle to be applied here is to keep the house closed during the day while providing as much through ventilation as possible during the night in order to cool down the house by means of the cold night air. It is important that the insulation is placed on the exterior part of the house and the heat capacity of roof and walls is large, so that the closed house is only warmed up slowly during the day.

In hot-wet climates the diurnal temperature changes are small. The indoor air velocity should be reasonably high both during the night and day in order to improve comfort. This can be obtained by natural ventilation if the house is placed in a suitable way in relation to the prevailing wind direction, and if the openings for ventilation are placed in such a way as to allow maximum velocities in the rooms. Several of the principles mentioned here have been investigated in the past in comprehensive studies by Givoni (1969)* and Van Straaten (1967)*. It should be noted that the application of these principles need not be expensive, some in fact are very inexpensive.

PRACTICAL APPLICATIONS OF COMFORT EQUATIONS

Fanger (1973f) summarized a number of practical applications of the comfort equations as developed by him and others. As no two subjects are alike, it is evident that these equations do not apply to everybody, however certain comfort conditions can be calculated which would satisfy the majority of people working in an office or factory. Studies

*See Fanger (1973c).

with 1300 subjects in Copenhagen have shown that only 5% of the subjects were dissatisfied.

Comfort diagrams can be prepared from the comfort equations. They can be applied to a subject if we know his or her activity level and the type of clothing he or she is wearing. Some of these diagrams are published by Fanger (1973f). Fanger also studied the influence of age. It has been suggested that the equations could not be applied to aged people. However, a study using several hundreds of subjects, varying in age between 18 and 90 years indicated that despite a great difference in thermoregulatory efficiency of these different age groups no difference exists in preferred ambient temperature.

It has been suggested by Bedford (1964)*, Humphreys (1970)* and Wyon (1968)* that different nationalities living in different countries would have different preferred ambient comfort temperature. Fanger repeated these studies in 1973 both with Danish subjects, with people from the USA and with subjects living all their lives in the tropics and who were tested 8 h after they returned to Copenhagen. Subjects of the three groups used the same standard clothing. No differences in comfort temperature were observed. According to Fanger *et al.* national differences in preferred ambient temperature seem to be exclusively a function of difference in clothing habits.

Further studies by Fanger and his colleagues, using large groups of male and female subjects, seem to suggest that no differences in preferred ambient temperatures are observed amongst different sexes (except during menstrual periods of female subjects), or during different seasons of the year. If differences do occur it is due, according to Fanger, to differences in clothing. Also differences between the hour of the day do not seem to influence the outcome of a comfort temperature test despite the fact that internal body temperature is high late in the afternoon and low early in the morning.

Studies by Tromp and Bouma between 1962 and 1970 at Leiden, The Netherlands, using individual subjects could not confirm the various, above mentioned, conclusions of Fanger *et al.* They may be true for large groups of subjects as a whole but not for thousands of individual subjects as many unforseen conditions arise; for example: menstrual cycles in females; periods preceding common colds; difficulties of many subjects to start work early in the morning; age difference between subjects; subjects suffering from meteorotropic diseases (asthmatics, rheumatics, heartpatients etc.), in fact all examples of circumstances in which subjects have a poor thermoregulatory efficiency. In families during meals that certain members of the family prefer a temperature of 20–21 °C whereas others are satisfied with 18 °C. It is true that the differences in preferred temperature are not great but 1 or 2 °C may make a great difference in subjective comfort

*See Fanger (1973c).

feelings. It is also not realized that climatic chamber experiment in a space with equally warmed walls is entirely different from a space in a room with exterior walls and windows. A temperature of the air of 20 °C may be comfortable in one particular well insulated space whereas other rooms with cold walls create as a result of reduced radiation great discomfort, particularly in older, slightly rheumatic subjects. This problem which was studied by McIntyre (1975c) and described as radiation draughts confirms our statement. Experiments of McIntyre have shown that discomfort may be experienced where the radiant temperature of a cold surface falls more than 8 °C below the mean radiant temperature in the centre of a room which is considered to be comfortable.

In our opinion comfort equations for the majority of office workers are, in general, very useful for the building services engineer whose job it is to construct large spacious offices or factories. One should, however, be very careful when applying these quations to private homes, or to individuals working in offices or factories with thermoregulatory efficiency differing considerably from the average population, e.g. asthmatics, rheumatics, allergic subjects etc. These subjects who represent several hundred thousand members of the community (asthmatics alone represent in W. Europe 1–2 % of the population) are not usually used for these laboratory experiments. Therefore the values obtained apply only to the perfectly healthy part of the community and should never be applied to the population as a whole.

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Observations (since 1971) on the Effects of Extreme Cold

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INCIDENCE AND CAUSE OF HYPOTHERMIA

Accidental hypothermia, as one disease of extreme cold, continues to occur in a variety of situations in spite of increasing knowledge about its incidence and prevention. People are being made more conscious of this condition as a separate entity; therefore more cases are being recognized and reported. However, it is frequently mistaken for death because of the areflexia of the corneal and pupillary reflexes and cardiac and respiratory arrest.

Hypothermia has been reported in a wide range of geographical locations. Not only does it occur in the colder environments but also in areas of high average environmental temperatures such as Texas (Coopwood and Kennedy, 1974), Israel (Cohen, 1977; Shapira *et al.*, 1975), Jamaica (Brooke, 1973) and other places where the temperature never drops below 16 °C (Sadikali and Owor, 1974).

Common causes of hypothermia continue to be old age (Watts, 1972; Goldman *et al.*, 1977; Irvine, 1974; Fox *et al.*, 1973a) which is frequently associated with poorly heated rooms (Meriweather and Goodman, 1972); exhaustion and exposure in mountain hiking or water immersion (Golden, 1973b; Hudson and Conn, 1974); alcohol consumption (Carter, 1976; Weyman, Greenbaum and Grace, 1974; Hudson *et al.*, 1974; Coopwood and Kennedy, 1974; Day and Morgan, 1974), barbituates (Hudson *et al.*, 1974; Shapira *et al.*, 1975); amphetamines (Lloyd, 1973; Yehuda and Wurtman, 1972); carbon monoxide (Hudson *et al.*, 1974) or other poisoning (Gautur *et al.*, 1972; Lloyd, 1973; Hudson *et al.*, 1974; Ary, Lomax and Cox, 1977), and infancy (Dominguez De Villota *et al.*, 1973; Hudson *et al.*, 1974; Yu and Jackson, 1974; Foray, Binder and Alonso, 1977; Theilade, 1977).

*Continuation of previous paper by M.B. Kreider (Tromp, 1977).

Additonal cases of hypothermia have been reported (Tafari and Gentz, 1974; Hirvonen, 1976; Wood, 1977; O'Keeffe, 1977).

Numerous medical conditions have been found with hypothermia, sometimes as a direct cause. Pathology of the central nervous system is one direct cause. Agenesis of the corpus callosum (Shapiro, Williama and Plum, 1969; Guikard *et al.*, 1972; Noël *et al.*, 1973; Editorial, *Lancet*, 1973; Vaisrub, 1973; Sadowsky and Reeves, 1975) or an associated defect in diencephalic development (Shapiro *et al.*, 1969) and diencephalic epilepsy (Fox *et al.*, 1973b) have been reported as a cause of hypothermia. Episodic or spontaneous periodic hypothermia appears to be due to these central nervous system defects yet not in all cases (Thomas and Green, 1973; Thomas, 1973). This is characterized by frequent periods of sweating, cutaneous flushing lasting 10–20 min, followed by the sensation of cold and shivering. Rectal temperature may drop to 34 °C followed by spontaneous rewarming. These episodes may appear only occasionally or many times in one day.

Likewise, Wernick's encephalopathy, damage to the hypothalamus (Philip and Smith, 1973; Lipton, Kirkpatrick and Rosenberg, 1977) and, in general, to some central mechanism (Johnson and Park, 1973) has also been reported. Other closely associated conditions are: myxedema (Maclean and Browning, 1974a, 1974b); diabetes (Weyman *et al.*, 1974; Matz, 1972); cerebral vascular accident (Lloyd, 1973); myocardial infarction (Weyman *et al.*, 1974; Hudson *et al.*, 1974); vascular surgery (Lewis and MacKenzie, 1972); abdominal surgery (Heymann, 1977; Kucha, 1974); malnutrition (Brooke, 1973); peptic ulcer (Hudson *et al.*, 1974); central glucopenia (Freinkel *et al.*, 1972; Mager, Robinson and Freinkel, 1976); fractured ankle (Lloyd, 1973); a quadreplegic individual during his hospitalization (Lloyd, 1973); generalized skin disease (Cucinell, 1978); a combination of drugs (lithium carbonate and diazepam for the control of aggressive behavior) (Naylor and McHarg, 1977); alpha methyl dopa for the relief of hypertension (Mohan and Johnson, 1975); and chlorpromazine administration (Sharma and Tikare, 1972).

In many cases hypothermia is accompanied by disease, whether or not the disease has contributed significantly to the hypothermia, but on the basis of a 6.5 % mortality among hypothermic alcoholics uncomplicated by disease, it is concluded that higher mortality rates are due to underlying disease (Weyman *et al.*, 1974; Hudson *et al.*, 1974). In any case disease greatly complicates the diagnosis and treatment of hypothermia.

The aged appear to be particularly prone to hypothermia. The incidence of hypothermia among the aged admitted to hospitals in Britain was found to be 3.6 % (Goldman *et al.*, 1977) which is higher than previously reported (Rep. Comm. Hypothermia, 1966). Reports continue to reaffirm that several factors contribute to this high susceptibility to cold among the elderly. These may include lower metabolic response to cold (Wagner, Robinson and Marino, 1974), and lower thermal sensitivity (Fox *et al.,* 1973a; Watts, 1972) resulting in less consciousness of the cold and poorer peripherial vasoconstriction (Wagner *et al.,* 1974, Collins *et al.,* 1977). However, not all older people have a poorer peripherial vasoconstriction (Horvath and Rochelle, 1977) but it is frequently found when measured in those who develop hypothermia.

Other predisposing factors in older people are severe undernutrition with wasting, almost complete lack of subcutaneous fat, anemia and hypoglycemia (Sadikali and Owor, 1974). While these physiological or medical conditions may contribute to hypothermia, social conditions are also frequently responsible (Donnison, 1977).

An increasing number of cases has been reported of apparent drowning in cold water of individuals, mostly young children (Dominguez de Villota *et al.,* 1973; Hunt, 1974; Theilade, 1977; Klarskov and Amter, 1976; Elliot, 1978) who have been resuscitated after 10–15 min of face submersion and have survived without detectable sequellae.

PHYSIOLOGICAL EFFECTS OF HYPOTHERMIA

A well known effect of cooling of tissues is a decrease in the metabolic activity of the tissue and thus a decrease in the utilization of energy and oxygen. This influences the concentration of metabolites and enzymes in the tissue and blood stream in unpredictable ways. While chemical changes have been increased during profound or surgical hypothermia, they are complicated by hypoxia due to surgical interruption of blood flow.

Blood sugar

A frequently observed change is an increase of blood sugar of 2–5 times the normal level. This may be due to increased blood insulin levels (Juffe *et al.,* 1977) which in turn may be due to decreased insulin production by the pancreas and/or to decreased peripheral utilization of glucose (Shida *et al.,* 1977). However, not all investigators find a consistant change in insulin concentration in hypothermia (Woolf *et al.,* 1972). High blood sugar comes back to normal by itself upon rewarming (LeRoith, Vinik and Jackson, 1974). In the rabbit brain, there seems to be no disturbance in the metabolism of ATP, ADP, CP, glycogen, glucose, lactic acid and inorganic phosphate during hypothermia where perfusion of blood is employed.

Hormone concentrations

Hormone concentrations do not change in a consistent direction. Cortisol concentrations in blood were low and utilization in the elderly was low during hypothermia (MacLean and Browning, 1974a) while 11-hydroxycorticosteroid concentrations were high (MacLean and Browning, 1974b). It appears that the hypophyseal-pituitary-thyroid axis is intact at rectal temperatures below 32 °C and that hypothermia is not a stimulus for release of thyrotrophic stimulating hormone (Woolf *et al.,* 1972); however, the level of PBI may influence rewarming (MacLean *et al.,* 1974c). Several enzymes have been studied during hypothermia but they do not change in a consistent direction (Altland, Highman and Sellers, 1974; Carlson, Emilson and Rapaport, 1978; Ramazzolto and Carlin, 1978; Ruchkina, 1976; MacLean *et al.,* 1974d).

Cardiovascular function

Progressive hypothermia is accompanied by changes in cardiovascular function such as sinus bradycardia, atrial fibrillation, prolongation of the QRS complex and the Q-T interval and development of the '*J*' loop or '*Osborn*' waves (Martinez-Lopez, 1976; Thomson *et al.,* 1977; Wenger and Mohelsky, 1972; Clements and Hurst, 1972; Nicolas *et al.,* 1975; Storch, 1976). This '*Osborn*' wave may appear as early as 35.6 °C but becomes marked at 26.7 °C and may be due directly to hypothermia and not acidosis (Thompson *et al.,* 1977) and belongs partly to the de- and repolarization phases (Pieda and Kenedi, 1973). It does not appear in all cases of hypothermia and is not limited to hypothermia (Thompson *et al.,* 1977; Weyman *et al.,* 1974; MacLean and Emslie-Smith, 1974). Sometimes there is an inversion of the T wave (Falk, Denlinger and O'Neill, 1977).

Blood flow

Blood flow decreases due to decreased cardiac activity, increased viscosity (Chen and Chien, 1978) and *erythro*cyte aggregation (Schmid-Schönbein *et al.,* 1973). Blood flow to individual organs has recently been measured. Kidney blood flow may decrease proportionately more than total flow due to a direct response to cold; however, autoregulation is maintained (Chapman *et al.,* 1975; Withey, Chapman and Munday, 1974; Withey, Chapman and Munday, 1976; Tempel, Musacchia and Jones, 1977). This decrease of blood flow reduces such functions as glomerular filtration (Withey *et al.,* 1976) and ultimately renal failure can develop (Kopsa, 1977).

Metabolism and function of nervous tissue

The metabolism and function of the nervous tissue is also reduced by hypothermia. Well known is the slow response to external stimuli, areflexia, and unconsciousness. Chemoreceptors in the medulla have a reduced response to hypercapnia (Ruiz, 1975); electrical activity of the cortex decreases (Moseley, Ojeman and Ward, 1972) and cell damage to the brain has been found under some conditions (Remis, Kapeller and Zlatos, 1974; Kapeller, Remis and Palongyi, 1974) but not under all conditions (Heckers and Gercken, 1974). In the rabbit, conduction velocities of peripheral nerves have been reduced (DeJesus, Hausmanowa-Petrusewicz and Barchi, 1973; Vanggaard, 1975) along with sympathetic nervous activity but some preganglionic neurons were still discharging below 25 °C (Kaul, Beard and Miller, 1973). At the moment, these isolated studies are hard to piece together into a unified picture.

REWARMING FROM HYPOTHERMIA

The importance of rapid rewarming following rapid or acute cooling seems to have evolved from the infamous Dachau experiments (Alexander, 1945) and has been supported by other 'acceptable' research of Hegnauer and Penrod (1950), Bigelow, Lindsay and Greenwood (1950), Behnke and Yaglou (1950) and summarized by Burton and Edholm (1955). Likewise, slow rewarming by natural body heat appeared to be better in cases of slow or chronic cooling to low temperature because it avoids the *afterdrop* of core temperature, the fatal hypotension or *rewarming collapse* or *shock*, and the serious imbalance between rapidly increasing metabolism and oxygen availability. (Slow rewarming is done mainly by the natural internal body heat, often assisted by mild surface rewarming). However, reports reveal that those distinctions between slow and rapid cooling have not always been maintained in practice and successes have been obtained at times under almost any type of rewarming. The aim of rapid rewarming after rapid cooling, as opposed to moderate rewarming, is to warm all tissues within a few minutes. This is to prevent the 'afterdrop' of heart temperature which can cause death, due to the return of cold peripheral blood to the heart.

1. *Immersion in warm water* (40–44 °C), one of the earliest methods of rapid core rewarming, is still an acceptable method wherever available. The arms and legs are not immersed in the warm water along with the trunk until considerable rewarming has occurred and the vital functions have stabilized. By holding the cold, hypoxic, and acidic blood in the extremities, this allows more rapid stabilization of vital functions at the most critical time (Meriweather and Goodman, 1972). However, there are some problems with water immersion.

For example it may interfere with adequate monitoring of the patient, or it may precipitate ventricular fibrillation and may seriously hamper cardiovascular resuscitation (Rueler, 1977).

Newer methods of core rewarming involve the breathing of warm saturated air, blood rewarming by a heat exchanger with or without an external pump, peritoneal dialysis or lavage, colonic infusion of warm water (Bonsing, 1977) and direct or mediastinal irrigation in severe cases (Coughlin, 1973; Ledingham and Mone, 1978).

2. *The warm saturated air method* was introduced (Lloyd *et al.*, 1972; Shanks and Sara, 1972) with the claim supported by others that the heat produced can amount to 30% of the heat production of a hypothermic patient and that it prevents the dangerous 'afterdrop'. Others have also found little 'afterdrop' (Lloyd, 1973; Lloyd and Frankland, 1974; Hayward and Steinman, 1975; Shanks, 1975; Collis, Steinman and Chaney, 1977). However, on the basis of the physics of heat transfer very little rewarming can be expected (Hudson and Robinson, 1973). Slightly more rewarming may be expected if helium is substituted for nitrogen in the inhalation mixture (Beran, Proctor and Sperling, 1975). But this method has been tried and appears to contribute little toward rewarming (Lloyd *et al.*, 1972; Auld and Norman, 1977; Bristow, 1977; Guild, 1977; Editorial, 1978a). It might have some value in preventing further body temperature drop through the respiratory tract, but mostly on the coldest days or possibly during surgery (Hudson and Robinson, 1973). There is some concern about potential heat burn which may occur with this method (Guild, 1977).

3. *The method of blood rewarming with an extracorporeal circuit,* oxygenator, and heat exchanger requires a trained team, availability of equipment and time for preparation, and has been used in some cases of hypothermia (Truscott, Firor and Clein, 1973; Towne, 1972; Wickström *et al.*, 1976). Arteriovenous shunts through heat exchangers without the use of pumps were also found to produce rapid rewarming and prevent an 'afterdrop' of core temperature (Gregory, Patton and McFadden, 1973).

4. *Peritoneal dialysis* or *lavage* is a method that requires little equipment or time delay and is highly recommended (Patton and Doolittle, 1972; Coughlin, 1973; Exton-Smith, 1973; Grossheim, 1973; Patton, Doolittle and Hamlet, 1974; Klarskov and Amter, 1976; Bristow, 1977; Bristow *et al.*, 1977; Bristow, 1978; Pickering, Bristow and Craig, 1977; Editorial, 1978b; Jessen and Hagelsten, 1978).

A laboratory comparison of these four methods of rewarming made on four young men cooled to 35 °C or below showed the order of effective rewarming to be immersion in warm water, a suit with water coils, inhalation of warm moist air and spontaneous rewarming (Marcus, 1978).

5. In spite of these generally accepted methods, active surface rewarming has been used or recommended in chronic hypothermia (Weyman *et al.,* 1974; Ledingham *et al.,* 1978). Surface rewarming may be tolerated better by the young than by the elderly (Discussion, *J. Roy. Nav. Med. Services,* 1973).

SUPPORTIVE TREATMENT DURING REWARMING FROM HYPOTHERMIA

In addition to the actual rewarming techniques, the supportive medical treatment may be most critical for survival in some cases. The sequence of treatment that appears most frequently in the literature (Editorial, *Resus,* 1972; Golden, 1973a; Mills, 1973a) is the following or a modification thereof:

1. *When hypothermia is moderate or early,* rewarming should be started along with ventilatory support such as 95 % oxygen, 5 % carbon dioxide, and treatment for ventricular fibrillation, if necessary. This may include electrical defibrillation, administration of calcium salts, adrenergic drugs and xylocaine or digoxin in lower than normal doses. However, vasopressor drugs are not recommended for use by all experts (Hamlet, 1978). Replacement of warm fluids is highly recommended. This may include plasma, blood, saline, glucose and other fluids. The longer and more severe the hypothermia, the greater the dehydration and hemoconcentration. An intravenous buffer such as a bicarbonate should be given to counteract the acidosis which generally develops. Hydrocortisone or some other corticosteroid may be helpful (Editorial, 1972; Ledingham *et al.,* 1978) but not in the elderly (MacLean and Browning, 1974a).

2. *When hypothermia is late, severe, and due to rapid cooling,* when respiratory and cardiac arrest are present, there is a need for circulatory support, such as external cardiac massage and respiratory support, such as endotracheal intubation, intermittent positive-pressure of oxygen and carbon dioxide, and intra-arterial injections of warm fluids (as stated in previous therapy statements). Drug therapy should not be started at this stage (Ledingham *et al.,* 1978; Editorial, 1972). After the cardiovascular and respiratory systems have been revived, treatment similar to that of the early hypothermic patient can be initiated.

3. *When hypothermia is late, severe, and has occurred over a long period of time* resulting in cardiac arrest or fibrillation, reactivation or defibrillation may not be successful until some rewarming has taken place. Any resuscitative action which causes any mechanical disturbance or stimulation of the heart may produce ventricular fibrillation or arrest. Such stimuli include: external cardiac massage, moving to an erect or sitting position, catheterization of the heart or blood vessels

and drinking or eating. However, not all clinicians find adverse effects of these kinds of manipulations (Ledingham *et al.,* 1978; Truscott *et al.,* 1973). Possibly the level of hypothermia may influence the response to manipulation. A warning is given by several people that one should not use difficult and dangerous treatment or overtreat the patient (Editorial, 1978b; Hamlet, 1978).

FROSTBITE*

Incidence

The incidence of frostbite remains high among individuals under the influence of alcohol (Jarrett, 1974; Kyosola, 1974; Weyman *et al.,* 1974; Rasmusen and Zook, 1972; Gralino, Porter and Rosch, 1976; Grossheim, 1973), mountaineers (Ward, 1974; Gralino *et al.,* 1976), and other outdoor people involved in an accident (Holm and Vanggaard, 1974; Gralino *et al.,* 1976), the mentally retarded (Jarrett, 1974: Kyosola, 1974), and a jogger (Hershkowitz, 1977). Other predisposing conditions for frostbite are trenchfoot (Kyosola, 1974), peripheral atherosclerosis (Gralino *et al.,* 1976), open wounds (Butson, 1975), wet skin (Molnar *et al.,* 1973), and possibly hypoxia of altitude (Nair *et al.,* 1977).

Some reviews suggest that the elderly are more susceptible to frostbite because of poorer mobility, poorer sensitivity to cold and wet; because of the existence of disease such as arthritis, and cardiac and central nervous system disorders (Boswick, 1976; Lane, 1975).

A new analysis of frostbite injury among American troops in the Korean military conflict (Sumner, Criblez and Doolittle, 1974) reveals that the following characteristics increase susceptibility to frostbite: (i) persons with lower rank, education and experience with the cold; (ii) those who smoked cigarettes, and (iii) Negroes, and Caucasians with type O blood. In a study of 298 cases, Negroes were 2.8 times more prone to freezing injury than their Caucasian counterparts. Several reasons for a greater Negro susceptibility have been recognized as less circulation to the extremities, less experience in the cold, and possibly, greater susceptibility of dark skin which has greater melanin pigmentation, to damage from frostbite (Post, Daniels and Binford, 1975).

Mechanism of frostbite

Many reviews have been written which include the mechanisms involved in frostbite (Ward, 1974; Welch, 1974; Lane, 1975; Boswick, 1976; Welch *et al.,* 1974; Jarrett, 1974; Dinep, 1975; Rasmusen *et al.,* 1972; Mills, 1973; Mills, 1976; Mazur, 1977).

*Editor's note: See also paper by Singh and Chohan p. 114, on frostbite at high altitude.

1. Some of the first processes occuring in exposure to cold are *vasoconstriction, increased permeability of the capillary* and *loss of fluids to the intercellular space.* This is accompanied by hemoconcentration, increased viscosity and sludging of the blood. Intercellular ice crystal formation develops and decreases the concentration of fluid or free water by drawing water from intracellular and vascular compartments. This dehydration of the cell results in hyperosmolarity and denaturation of proteins and enzymes and death of the cell.

2. *Intracellular ice crystals* may also form. There seems to be an inverse relationship between the amount of intracellular ice formation and the degree of extracellular supercooling and the rate of cooling (Diller, 1975). This rate of cooling has again been implicated in the amount of damage done (Sjoström, 1975; Nei, 1976a; Nei, 1976b). Intracellular ice can result in distortion and rupture of various cellular components. This includes damage to endoplasmic reticulum and ribosomal arrangement (Rabb *et al.,* 1974; Sherman and Liu, 1973), to the nucleus (Mikhailov, 1976), to the mitochondria (Rabb *et al.,* 1974; Bowers *et al.,* 1973; Mikhailov, 1976) and to the cellular membrane (Mikhailov, 1976; Bowers *et al.,* 1973; Rabb *et al.,* 1974; Meryman, 1974). While the cellular membrane may be damaged in freezing it also is important in controlling the amount of damage due to freezing as summarized in a previous volume of this series (Kreider, 1977) and by Mazur (1977).

3. *Damage to venules and capillaries* may also occur (Rabb *et al.,* 1974; Cummings and Lykke, 1973a; Dinep, 1975) accompanied by hemostasis due to aggregations of embolic platelets. These aggregates may disappear for some 50–60 min but hemostasis occurs later due to destruction of the epithelium (Rabb *et al.,* 1974; Chohan, Singh and Balakrishnam, 1975). Electrophoretic motility of platelets is lower in the cold (Ando, Steiner and Baldini, 1974).

Treatment

1. The accepted treatment of frostbite has been influenced much by Dr William Mills, Jr, of Ankorage, (Washburn, 1962; Mills, 1973b; Mills, 1976; Bangs *et al.*, 1977b; Bangs, Hamlet and Mills, 1977a) and was summarized in the earlier edition of this series (Kreider, 1977). Many other authors agree with this basic treatment, sometimes with slight modification (Boswick, 1976; Ward, 1974; Jarrett, 1974; Kyosola, 1974; Riedler, Holzl and Flora, 1976; Welch, 1974; Welch *et al.*, 1974; Arledge, 1973; Dinep, 1975).

This modified treatment is as follows: When the tissue is frozen, regardless of the depth or severity of the injury, rewarming should be rapid, in water of 38–42 °C. This has been verified experimentally in the hind limbs of rabbits (Snider *et al.,* 1974). An alternative is to start with water at about 10 °C and gradually increase the temperature to 42 °C in about 30 min. This technique may reduce or prevent the pain of thawing (Bangs *et al.*, 1977b). When the tissue is no longer frozen at the time that treatment starts, slow rewarming in air should be used. Additional care includes use of sedatives and analgesics, prevention of mechanical contact and use of sterile techniques including isolation and use of masks. Extremities should be cleansed for 20 min twice daily in a whirlpool at 32–37 °C using a mild disinfectant soap. The motion of the whirlpool is also important in the natural debridement of any blebs and other dead tissue. At the same time it produces movement of the damaged part and helps to reduce the amount of constriction from scar tissue.

2. *Surgical sympathectomy*, used much in the past, appears to produce the following results, (i) more rapid resolution of infection, (ii) more rapid loss of hyperhidrosis, (iii) less edema and pain, (iv) more rapid appearance of sensation, and demarcation of tissue, but less preservation of tissue (Mills, 1973). A new method for producing a sympathetic blockade is the intra-arterial injection of reserpine. Vasospasm is relieved, possibly due to depletion of norepinephrine in the vascular wall (Porter *et al.*, 1972; Snider *et al.*, 1974), and normal limb sensations return without the return of pain (Porter *et al.*, 1976). Another report (Kyosola, 1974) suggests that 'ordinary' paravertebral sympathetic blockages were not effective but Marcain adrenalin injected into the paravertebral space provided rapid healing and relief of pain. Another drug, a corticosteroid called flurandrenolide, has appeared to reduce inflammation and encourage healing in spite of the known vasoconstrictive effect (Kobak, 1975). In rats (Cummings and Lykke, 1973b) and in rabbits (Talwar and Gulati, 1972) other non-steroidal anti-inflammatory drugs have been used with some success.

3. Certain special treatments may be needed at times. Both antibiotics and tetanus toxoid should be used only if there is deep infection or noticeable damage (Mills, 1976; Jarrett, 1974). Other treatments which have shown great promise but are not used now as much as earlier are low molecular weight dextran, surgical sympathectomy, heparin, and hyperbaric oxygen (Bangs *et al.*, 1977b; Holm and Vanggaard, 1974; Rasmusen *et al.*, 1972) A rather rare after effect of frostbite has been cancer (Katsas *et al.*, 1977).

4. Attempts have been made to develop prognostic tools for frostbite injury with varying degrees of success. Among the methods tested were conventional X-ray (Fishler, 1972), angiography (Erikson and Ponten, 1975; Gralino et al., 1976), radiopharmaceutical scintiscan (Lisbona and Rosenthall, 1976), electromyography (Marshall, 1972), and thermography (Hamlet *et al.*, 1977).

OTHER DISEASES OF COLD

Trenchfoot and *immersion foot* which can occur at above freezing temperatures can produce injury just as debilitating as frostbite. The incidence of occurrence increased greatly during World War II and in the Korean conflict; only small numbers of cases are reported among civilians and in peacetimes (Shields, 1972).

Another condition due to prolonged or repeated exposure to cold is *cold induced digital epiphyseal necrosis* in childhood, and may appear 6–8 months after exposure. The clinical symptoms are initial joint pain and restricted movement of the fingers. Later developments may include angulatory deformities, arrested growth with shortness and weakness of fingers due to destruction of chondrocytes and ischemic necrosis of osteocytes (Hakstian, 1972). Another conditions involving the hand is extensor tenosynovitis (Georgitis, 1978).

In addition, various cold sensitivities have been identified which may be due to an isolated idiosyncracy or to preexisting disease. *Raynaud's phenomenon* involves a prolonged vasospasm initiated by a very slight exposure to cold and may be excited by occupational poisons or various medical conditions (Editorial, Brit. Med. J., 1975). *Chilblains* or *acute pernio* may result from cold-wet exposure, especially in young girls (Coskey and Mehregan, 1974; Tring, 1977; Fujimori *et al.*, 1976). This condition may be characterized by the sudden appearance of red itchy swelling at the first approach of cold weather. Lesions or blisters may develop on the dorsal surface of hands and feet which, if broken, may leave slow healing ulcers (Coskey and Mehregan, 1974; Cummings *et al.*, 1973b) and patches of bluish-red discoloration which vary with the elevation of the hand or foot. In some cases arteries are infiltrated by special blood cells, the walls of the arteries will thicken and proliferation of the intima layer leads to occlusion of the lumina. Suggested treatment is elevation, rest and salicylates (Coskey and Mehregan, 1974).

An allergic reaction producing *cold urticaria* is another response to cold. Weals develop at the site of local cooling (Eady and Greaves, 1978; Soter *et al.*, 1977) increased stomach acidity occurs, and there may be evidence of increased histamine release (Lass, 1978). Sometimes anaphylaxis develops producing the condition called Schonlein-Henoch syndrome (Roger *et al.*, 1971). Another rare group of symptoms reported includes *anaphylactic purpura, arthralgia, abdominal pain, gastrointestinal bleeding* and *nephropathy*. *Cryofibrinogenemia* can also develop (Griswold *et al.*, 1973; Goodall, 1975). A *cold urticaria* due to an autosomal dominant condition is found rarely. This condition which precipitates urticaria or macular erythema is associated with general malaise, aching joints, and shivering (Editorial, *Brit. Med. J.*, 1975).

And finally, other rare diseases associated with cold are *paroxymal cold hemoglobinuria* and *cold hemagglutinin* (Bird, 1977).

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Developments in Architectural and Urban Biometeorology (since 1973)

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INTRODUCTION

Since 1973, one issue seems to have dominated architectural and urban planning: concern for the future availability of energy supplies. Although forecasts as early as the 1950s predicted that shortages in petroleum supplies could occur in the 1970s (Hubert, 1949), little concern for energy efficient building designs was evident.

During the two decades before 1973, open space, ease of operation, flexibility, and low first-costs resulted in architectural styles that were essentially insensitive to climatological effects or to the source of fuel supplies. Though costs of operation were sometimes considered, they did not serve as primary design criteria. Costs of fuel and electrical power increased at no more (often less) than the rate of inflation. Thus, more concern was expressed over the levels of comfort and luxury that could be provided by design. Lighting levels were increased. The numbers and sizes of appliances and home entertainment centers were increased. Heating systems were selected to provide maximum comfort, even during the most severe weather. Central cooling systems were also installed in most newly designed facilities. All of these features increased our comfort conditions, but they are energy intensive.

During the 1960s and early 1970s, concern for environmental protection further aggrevated the coming energy problem. Existing coal-fired electrical power plants were converted to natural gas or petroleum to reduce air pollution, moratoriums were placed on the construction of nuclear reactors, and air pollution control devices were required on automotive equipment. Cooling towers were required for power plants and industrial processes, and coal-fired industrial furnaces were replaced with electrical furnaces to further reduce air and water pollution.

Although these efforts may have improved the quality of air and water, they were also energy intensive and increased our energy requirements. The resultant increase in energy consumption patterns are shown in Fig. 1 (Brown, 1976). Brown-outs and black-outs experienced during this time prefaced the seriousness of this increase in energy consumption. Unfortunately, these shortages were generally viewed as short-term (i.e. peak-load) problems that could be rectified by increasing the installed capacities of the generating plants, rather than long-term problems that should be relieved by changes in energy use patterns. Of particular interest though, were the proposed short term solutions which included off-peak utilization of industrial power, resetting of thermostatic control of space cooling systems during peak loads, load-shedding of 'unnecessary' electrical loads, and reorganization of residential energy use patterns to reduce daytime requirements. Many of these concepts are now being considered 'energy conservation opportunities' (Federal Energy Admin., 1977).

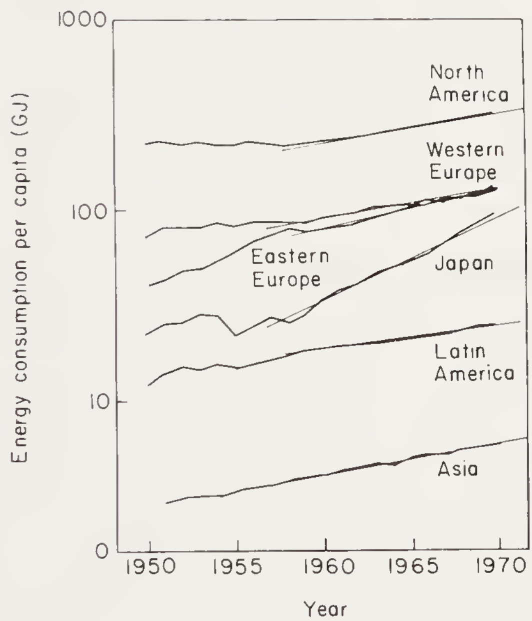

Fig. 1. Per capita energy consumption adapted from Brown, 1976. (GJ = gigajoule)

Another result of the increased energy consumption was the discovery of 'heat islands'. As reported by Givoni (1973), studies appeared in the literature in which attempts were made to correlate changes in meteorological factors (i.e. temperatures and pressures, etc.) with urban characteristics (i.e. urban sizes, populations, density of buildings, etc.). A further indication that energy consumption rates were not directly considered in environmental impact statements or in building design is found in the review where Givoni listed nine features of planning which deserved further study to determine if they significantly affected quantitative relationships between regional and urban climates. Conspicous by its absence was the energy consumption rate.

Although we received these early warnings of the approaching energy shortage, we did not really pay much attention until the oil embargo of 1973. Regardless of the political overtones of this action, the effect served as a warning that our energy resources were, indeed, finite. As a result, we have seen a dramatic and probably irreversible change occur within building design since 1973.

Some trends in design that have developed in the last six years include: (i) Reduced heat transmission through the building envelope; (ii) reduced infiltration through windows, doors and construction connections; (iii) utilization of new materials; (iv) renewed interest in solar energy; (v) renewed interest in electrical heat pumps; (vi) rediscovery of the values of daylighting; (vii) improved appliance efficiencies; (viii) improved methods of energy calculations; (ix) new energy codes and standards; (x) maintained requirement for environmental protection. These trends will be discussed in this paper by focusing on five topics: (i) energy management in new and existing buildings; (ii) quality of life and energy requirements; (iii) energy resource alternatives in buildings; (iv) comfort and health implications; and (v) economic implications.

ENERGY MANAGEMENT IN NEW AND EXISTING BUILDINGS

Immediate responses to the 1973 oil embargo were to minimize energy consumption. Orders were issued for thermostats in existing buildings to be lowered to at least 20 °C (68 °F), for ventilation systems to be adjusted to minimum rates, for systems to be de-energized in unoccupied spaces and for lights to be turned off wherever possible. 'Weatherization programs' were also recommended by various agencies. These programs stressed insulation of walls and ceilings and the sealing of sources of infiltration. Estimated energy reductions resulting from these operational changes have ranged from 5 to 25% in various buildings (Publ. NBS, 1973). Long lists of possible energy reducing measures were propagated, but little supporting evidence existed that many of the suggestions would reduce energy consumption. Thus, when an energy consumption measure was reported to have reduced consumption in a particular case, generalizations were often made and similar changes were attempted in buildings which were of different sizes and configurations and which served different functions.

Results of implementing these first energy conservation measures under near-crises conditions varied considerably. Reports of energy savings exceeding 50% were common. Conversely, that same energy conservation measure implemented in another building may have caused an increase in energy consumption. Some examples of misapplications of energy conservation measures are cited below:

(i) Reduction of lighting in buildings which were designed to utilize recovered heat from the lighting fixtures to provide heat in other zones by heat pump systems;
(ii) Reduction of ventilation rates in systems which were designed to use outdoor air in mixed air systems for space cooling when advantageous.
(iii) Insulation of buildings to reduce heating loads but failure to resize the capacity of the heating systems to match the reduced load.
(iv) Sealing of air leaks in buildings but failure to provide alternative sources of required combustion air for heating systems.

Some of the misapplications not only caused increased energy consumption but they also caused health and safety problems for the occupants.

Although misapplications did occur, many safe and effective measures were implemented. From these experiences, several new and important concepts are now being used in the design of new buildings and the management of existing buildings. One of the most important concepts developed to evaluate the energy performance of buildings is the energy utilization index (EUI) which accounts for all sources of energy used in the building as a function of the gross floor area of the building (Hittman Assoc., 1977); because of its simplicity, it was readily accepted and used to evaluate the performance of new and existing buildings (Dubin, 1974). The EUI also served as a basis for the development of new energy codes and standards.

The simplicity of the EUI is also one of its greatest weaknesses. Unless additional information is provided, the EUI is not sensitive to geographic location or building function. To account for geographic location, the EUI is often divided by the annual degree-days (DD). To account for various building functions, the building category may be specified (Publ. Amer. Inst. Arch., 1978) or the EUI may be divided by a functional figure of merit (i.e. patient-day, man-hours per day, etc.) (Reynolds, Smith, Hills, Inc., 1974; Stroeh and Woods, 1978).

Division of EUI by annual degree-day (EUI/DD) provides an energy performance index which works reasonably well for small buildings which are dominated by envelope thermal loads (e.g. single family residences), and allows simple comparative analyses of building performances in various regions. The value EUI/DD is often used in literature concerning passive and active solar energy heating systems (Anderson, 1977). However, concern has been expressed that the degree-day concept, which is based on a 18.3 °C (65 °F) neutral temperature may not be appropriate for well-insulated small buildings or buildings in which the internal thermal loads are significant (Spielvogel, 1978).

The energy indices described so far only provide data based on annual performance. For energy management purposes, it has also been necessary to develop performance indices based on monthly or even daily data. One such index, the management energy utilization (MEU) index, developed for the US Veterans Hospital Administration (Reynolds, Smith, Hills, Inc., 1974), provides a monthly value of energy consumed per unit floor area per degree-day. The most serious problem with this index is that sensitivity of the relative performance of the building is lost during mild weather (i.e. at small values of monthly degree-days), since the energy values are divided by numbers close to zero. An evaluation of monthly data for larger buildings, such as hospitals, typically results in profiles shown in Figs. 2 and 3. As seen in these figures, the total monthly consumption during mild weather is less than the maximum for the year (Fig. 2), but the MEU values are maximized during these conditons (Fig. 3). This result is unfortunate, since the mechanical equipment will only be partly-loaded and thus will be operating at less than design (steady-state or full-load) efficiencies during the periods when the least amount of information can be derived from the MEU.

To eliminate this problem of insensitivity during part-load conditions, a building energy management index (BEMI) has been proposed (Stroeh *et al.*, 1978; Woods and Peterson, 1978). The BEMI does not use the conventional degree-day concept but relates the climatic conditions to energy consumption by referencing a temperature, −40 °C

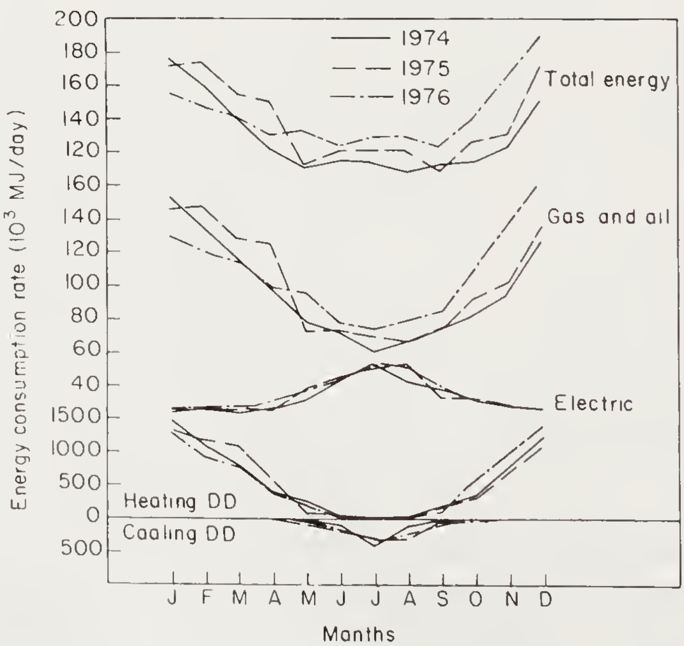

Fig. 2. Energy use in hospital A. (MJ = megajoules)

(−40 °F), which was chosen to be lower than normally expected for design winter conditions, but not so low that sensitivity to climatic influences is lost. Another feature of the BEMI is the inclusion of the

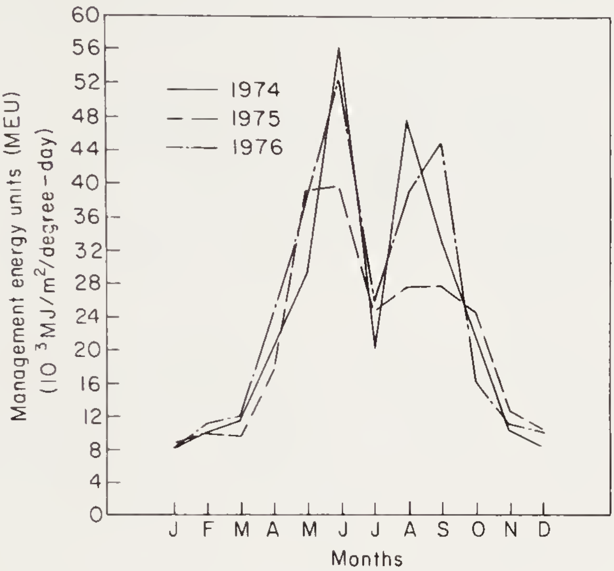

Fig. 3. Management of energy usage for hospital A.

occupancy load as a variable. Thus, the BEMI consists of a building energy characteristic (BEC) and a building function characteristic (BFC) which have been shown to be related linearly (Stroeh *et al.*, 1978; Woods *et al.*, 1978).

The BEMI (or in this case hospital energy management index, HEMI*) is shown in Fig. 4 for the same energy records shown in Figs. 2 and 3.

Since the winter data generally appear toward the upper right of Fig. 4 and the summer data to the lower left, the energy management objective may be stated as attempting to decrease the slope of the line without causing an increase in the intercept.

The building energy indices described above generally serve three functions:

(i) Provide feedback information on relative performance of an existing building as a function of time. Thus, evaluation of the success of energy conservation opportunities, which have been implemented within the building, may be made.

(ii) Provide feedback information on the performance of several existing buildings during the same period of time. Thus, management decisions can be made regarding potential investments in energy conservation.

*The HEMI differs from BEMI; the occupancy is accounted for as 'patient days', a value obtained from hospital daily records.

(iii) Indicate projected values of energy consumption to be established for new buildings which are to be designed. This function serves as the basis for the building energy performance standards (BEPS) which are now in the proposed rule-making stage (Dept. of Energy, 1978).

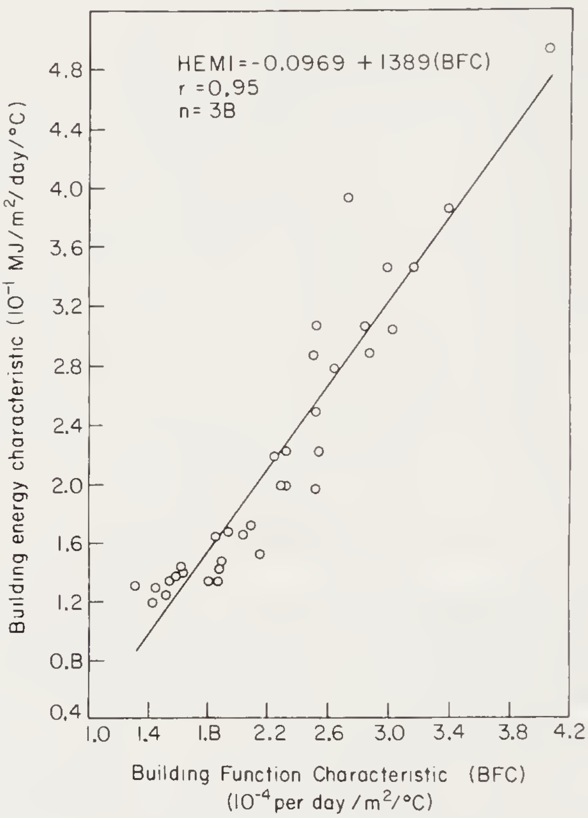

Fig. 4. Hospital energy management index for hospital A.

Thus, during the last six years, the concept of building energy management has progressed from a potential instrument to a valid reality. New buildings are no longer only evaluated at winter and summer design conditions. It is now possible, and mandatory in many communities,* to perform annual energy calculations, to project the energy consumption for the proposed building and to compare the results with reference or 'standard' data.

To achieve these projected energy consumption rates in a new building, the information that must be obtained includes: (i) climatological data; (ii) functional characteristics of the building; (iii) thermophysical properties of the building; (iv) performance characteristics of environmental control systems; (v) projected availability of energy resources proposed in the building design.

*Building Energy standards often require annual energy calculations.

When the appropriate data have been collected, the building energy performance may be calculated. For many years, the degree-day method was used to estimate heating energy requirements; but for the reasons described previously, the results for an individual building are subjected to large errors. Two methods have been conventionally used to estimate total seasonal cooling load requirements, the cooling-degree day method* and the full-load running-hours method.** With the advent of commercial programs, mini- and micro-computers and the programmable hand-held calculators, it is no longer necessary or practical to use these simplistic methods. If pre-packaged programs are not practical, published algorithms may be used to obtain hour-by-hour calculations of building system performance (Publ. Amer. Soc. Heat, 1975).

Today, the problems in energy calculations are not centered around the possibility of computing annual energy consumption rates, but around the efficiencies of computer programs that can be obtained without sacrificing the desired accuracies. Thus, a major area, indicated by Givoni to be in need of future research, has seen much improvement in the last six years, but much more investigation is needed.

QUALITY OF LIFE AND ENERGY REQUIREMENTS

A first impression that generally resulted from the energy conservation efforts immediately after the oil embargo was that a reduction in energy consumption required a compromise in the quality of life. Indeed, for a period of time (1974), many sacrifices were made which resulted in some dramatic reductions in energy consumption.

Unfortunately, the connotation of sacrifice or deterioration of 'life style' as a result of conservation practices has continued. However, a study of the Swedish experience since 1973 indicates that this apparent cause-and-effect need not exist. In 1973 Sweden had a per capita gross national product (GNP) nearly identical to that of the USA, yet the Swedish per capita energy consumption was 50% of that of the US (Schipper, 1976). At that time, the Swedish energy growth rate was 4.5% per year which was nearly identical to that of the US In 1975, a Swedish energy policy was adopted which stated that energy consumption could not increase more than 2% annually from the base year of 1973 (Hambraeus and Stillesjö, 1977). To date that program has been successful and the per capita GNP now surpasses that of the USA.

As if to reinforce the Swedish experience, four modern energy theorists of cultural evolution have been cited by Nader and Beckerman

*Cooling-degree day is defined as the compliment of the heating degree-day, with 18.3 °C (65 °F) as the neutral temperature.

**Full-load running hours are based on tabulated data.

(1978). The consensus of the theorists' opinions was that the amount of energy available constrains possibilities for social action, but no close coupling exists between the magnitude of energy use and the quality of life (Cottrell, 1955; White, 1959; Odum, 1971; Adams, 1974). However, as Odum (1971) suggests, the quality of life may in some way be dependent on the presence of feedback loops by which energy flows are controlled.

Within the scope of architectural biometeorology, an example of the pressures between these issues can be cited in regard to window treatment. Some researchers have indicated that energy can be reduced significantly by reducing window areas in buildings; however, others have indicated that adverse psychological reactions can be expected if visual contact with the exterior environment is lost (Collins, 1975). It is, therefore, reasonable to assume that windows are desirable, but the location and treatment of the windows should be designed to minimize their energy requirements.

The use of reveals, exterior shutters, double-pane glazing and interior drapery can all be used to reduce energy consumption. Moreover, windows provide daylighting and, if properly designed, can reduce the requirement for artificial lighting (Dean and Rosenfeld, 1977; Kusuda and Collins, 1978). Daylighting also serves as a form of passive heating, thus reducing the need for depletable energy sources.

These and other architectural treatments of the building envelope, such as sufficient wall and roof insulation, have resulted in a resurgence of regional architecture. New and exciting designs have been presented since 1973 in which response to local climatology is reflected. However, more studies are needed in the area of energy efficient architectural design and its impact on the quality of life.

ENERGY RESOURCE ALTERNATIVES IN BUILDINGS

The probability is high that we will deplete our resources of natural gas and oil within the next generation, unless conversions are made to other sources of energy for use within buildings. The most obvious alternatives are nuclear, coal, electricity and solar energy. The likelihood of using nuclear energy or coal in buildings, directly, is small. However, nuclear and coal-fired electrical plants, which could supply the energy needs, may be the most likely alternatives.

A common concept is that while the electric alternatives are practical, they may not be as efficient as combustion systems. As shown in Fig. 5, this assumption is not always correct (Woods and Donoso, 1977). For example, at 1973–74 effective supply efficiencies, the overall energy conversion efficiency for space heating, with a natural gas-fired furnace efficiency of 65%, would be approximately 43%. However, if this same natural gas resource were supplied to an electrical generating plant with a conversion efficiency of 32 % and the electricity was supplied to a house with a transmission efficiency of 91 %, and the electricity supplied a heat pump with a coefficient of performance (COP) of 2.5, the overall conversion efficiency for space heating would be approximately 49 %. Moreover, if strip-mined coal were burned at the power plant, the overall energy conversion efficiency for space heating with the heat pump would be approximately 53 %, which is significantly more efficient than using combustion furnaces. Conversely, other alternative sources, such as deep-mined coal or nuclear fuel, would result in overall energy conversion efficiencies for space heating with heat pumps less than those expected with a gas-fired combustion system.

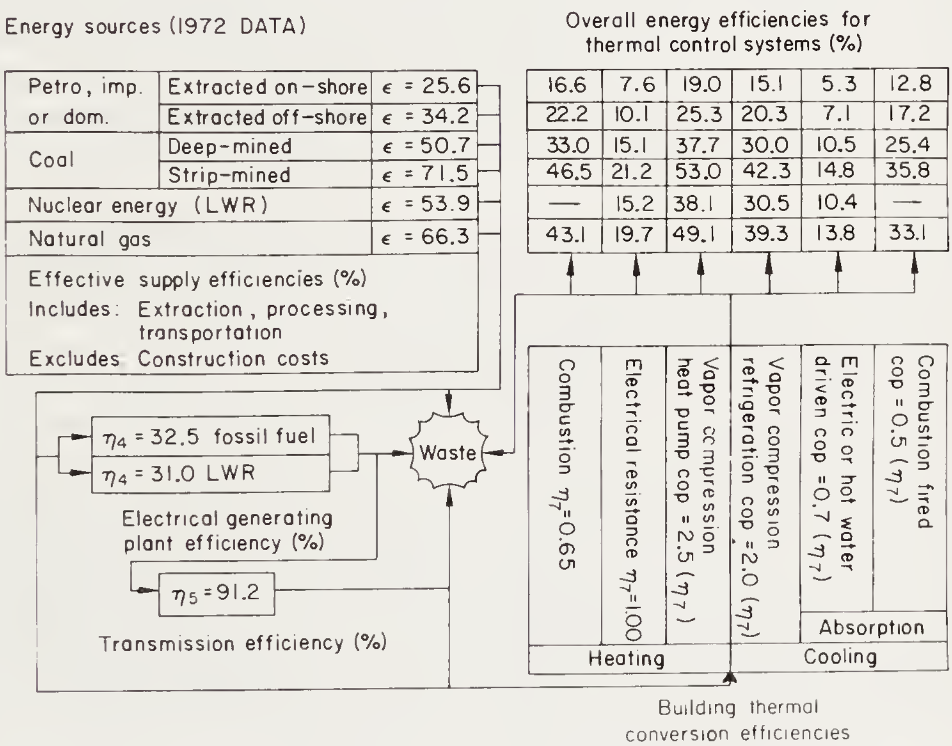

Fig. 5. Overall energy efficiences for thermal control in buildings.

Recent trends in new building construction have been toward electric heating, as natural gas has not been available in some areas and petroleum supplies or costs have not been stable. This trend is likely to continue. The overall energy conversion efficiency may not be changed by this fact alone, however, since a problem is apparent. We are now nearing peak capacities of power plants throughout the world. If a general shift to an electric heating economy continues to occur, peak generating capacities will probably be exceeded in climates with significant heating seasons, as 50–100 % more energy is generally consumed in the heating season than in the cooling season. Therefore, without careful planning and management of environmental control systems, traditional peak electrical outputs in summer could shift to winter periods. Time-of-day shifts could also occur from daytime summer hours to night-time winter hours. These shifts have already occurred in many parts of the world, including parts of Britain, Germany and the US.

To control these winter peaks, electrically heated ceramics or brick storage units have been used in Britain and Western Europe for many years (Asbury *et al.*, 1977), and domestic hot water storage systems are common throughout the world. However, since 1973, a renewed interest in these devices has been seen.

Other methods to reduce requirements for depletable energy resources also have been intensively studied since 1973. The primary alternatives to the conventional resources include solar energy, wind, geothermal and tidal (or wave) energy. Of these, solar energy systems have so far proven to be the most practical for general application in buildings.

Solar hot water heating systems have been used throughout the world since the turn of the century (Meinel and Meinel, 1976). However, the popularity of these systems decreased in the 1950s and 1960s as the cost of natural gas, petroleum and electricity decreased. The incredible increase in fuel costs (40% since 1973) has reversed that trend. Today, solar energy accounts for a measurable amount of the energy requirements in Israel, Japan, and India. Also, the US Department of Energy estimates that solar energy may contribute between 16% and 24% of the total energy mix in the US by the year 2000 (Public Domestic Policy Review Intergrity, Group, 1978). Solar energy is being used in buildings today for three primary functions: domestic hot water, space heating and space cooling. For each of these applications, 'passive' and 'active' methods are employed. The definitions of these methods are generally agreed to be:

Passive: little or no depletable energy resources required to operate the system

Active: significant amounts of depletable energy resources required to operate the system.

To quantify the distinction, Yellott (1977) has proposed that passive systems must operate with a COP of more than 50 (i.e. useful heat output must be at least 50 times more than the depletable energy resource required to provide the useful heat).

The most common examples of passive solar heat systems have been categorized into five generic types (Anderson and Michal, 1978; Balcomb, 1976).

(i) *Direct gain systems,* such as windows, ovcrhangs, drapes, and shutters which allow solar heat gain to be increased or decrcased as functions of time of day and time of year.

(ii) *Convection loops,* such as thermosiphon hot water heaters, use natural convection forces, derived from absorbed solar energy, to distribute the heat to desired locations.

(iii) *Thermal walls,* such as Trombe walls constructed of concrete, brick or adobe, and water walls, are designed to absorb solar radiation, store the energy in their mass and distribute the heat to the occupied space by radiation and convection.

(iv) *Roof ponds*, which are similar to water walls but located on the roof rather than south facing walls, have been reported to provide some cooling effect by a combination of night radiation and convection and evaporation from the exposed water surface.

(v) *Greenhouses*, attached to occupied spaces, can assist in space heating. They also can act as thermal buffers and can provide some humidity and air quality control in the occupied spaces.

Applications of passive systems have been practiced for centuries in indigenous and vernacular architecture. However, the principles involved in these systems seldom were objectively studied before 1973. Some analytical work has been reported since then, but additional research is needed, as optimum utilization of passive systems requires that thermal capabilities closely match the thermal requirements of the systems.

Active solar energy systems have been intensively studied since 1973. The most common applications of them have included: domestic hot water; space heating; and space cooling.

Most of the domestic water heating systems have been reported to use a liquid, such as water, to transfer the heat from the collectors; space heating systems have commonly used liquid or air for heat transfer and space cooling systems generally use water (Jordan and Liu, 1976).

In each of these systems, storage devices are often required. The most common storage media include: solids, such as rocks, packed beds, soils, and parafin wax; and liquids, such as water and salt solutions. Both solid and liquid types of storage media can be selected for sensible heat storage or phase-change characteristics (Jordan and Liu, 1976).

A storage device is generally used in a solar energy system whenever increased reliability of the performance of the system is desired. While some suggestions have been reported on methods to calculatc storage requirements (Duffie and Beckman, 1974; Klein *et al.,* 1975), research is still required.

Weather data are available for only a small percentage of cities throughout the world. If solar energy systems are to receive general acceptability, solar radiation data must be made more readily available. To obtain statistically reliable data, records for several years are required. Meantime, methods for estimating the required factors must be developed. Other design criteria to be considered include the required duration of storage, acceptable temperature ranges, and longevity of storage media.

Another area of general concern today, is the requirement for auxiliary or back-up energy resources. If sufficient solar energy could be collected and stored, auxiliary systems would not be required. However, to provide such capacity is usually not economically feasible. It is, therefore, desirable to couple solar energy systems to conventional systems, in ways that minimize the requirements for depletable energy resources (Van't Land, Woods and Peterson, 1978).

If solar energy utilization can continue to be developed at the rate seen for the last six years, and if conservation efforts can continue to be implemented, then the possibility is improved that energy demand and supply requirements may be balanced before the quality of life is degraded.

COMFORT AND HEALTH IMPLICATIONS

As stated previously, there is no reason to assume that energy efficiency implies compromises to either comfort or health. Some design features will actually enhance thermal comfort while other features could have negative implications if care is not taken to compensate.

An example of design features which can enhance comfort is the well-insulated wall. Since it more effectively resists heat transfer, the inside surface temperature is elevated in the winter and decreased in the summer compared to conventional wall systems. Thus, the amount of radiant heat exchange between the occupant and the wall is decreased in the winter and increased in the summer. Since the human body is as sensitive to radiant heat transfer as to convective heat transfer, the air temperature can be decreased 1 °C for each 0.7 °C that the mean radiant temperature is raised (McNall and Schlegel, 1968). Note that the converse is true in summer. For each 1 °C that the air temperature can be lowered, an energy savings of 5–10 % can be expected in climates with extensive heating seasons. So, it might be said that insulation saves twice; once as it retains the heat in the occupied space, twice when it allows the air temperature to be reset without adversely affecting thermal comfort.

Energy efficient designs can also cause deleterious effects if care is not taken to properly control the environment. In conjunction with adding insulation, we are constantly admonished to caulk and seal windows, doors and cracks to prevent or reduce infiltration. This is an effective method to reduce energy consumption, but care must be taken to insure that proper ventilation is maintained within the occupied space. If combustion systems are used in the building, care must also be taken to ensure that sufficient combustion air is provided. Several cases of asphyxiation have been reported in new or retrofit housing due to incomplete products of combustion being backdrafted into the occupied spaces (Hollowell and Traynor, 1978). If combustion systems are provided with separate, outdoor air supplies, this problem is usually solved.

Other problems regarding the quality of indoor air in energy efficient housing are less obvious and sometimes more difficult to solve. Outgassing of vapors from materials (building materials, furniture, cabinets, furnishings, etc.) and generation of gaseous and particulate contaminants by occupants are primary sources for nuisance or toxic levels of concentrations. Some of these contaminants have existed in housing for several years, but infiltration air was sufficient to dilute the concentrations to values that were acceptable. However, in energy efficient designs, explicit methods are often required to provide acceptable indoor air quality. Some examples of these sources are:

(i) Generation of unacceptable levels of total suspended particulate (TSP) concentrations from cigarette smoking. In an energy efficient house, one cigarette per hour may cause TSP concentrations to exceed values recommended by the World Health Organization ($100\,\mu g/m^3$). However, an electrostatic filter in the return air system can easily clean the air to acceptable levels (Brundrett, 1975; Woods, 1978).

(ii) Vapor outgassing of formaldehyde from materials like particle board (Andersen, 1975). The most successful method of controlling this contaminant is probably dilution air which can be introduced into the heating and cooling system in controlled but sufficient rates to maintain a concentration within acceptable levels.

(iii) Outgassing of radon from concrete and masonry (Budnitz *et al.*, 1978). Again, the most successful method of control is introducing sufficient air for dilution.

Thus, as more energy efficient architectural designs have been introduced, accurate control of the indoor environment has become a necessity. In some cases, adaptation of currently available control technology has been adequate to maintain healthy and comfortable conditions. However, in other cases, new technologies have been required, such as the development of intermittent and variable ventilation control systems (Kusuda, 1976; Ogasawara, Taniguchi and Sukenira, 1979). Concentrated research efforts will continue to be required in this field.

ECONOMIC IMPLICATIONS

As the costs of fuels and electrical power have dramatically increased over the last six years, so has awareness of the relative importance of owning and operating costs relative to first cost of buildings. The concepts of life-cycle-costing is now being taken seriously and, in some cases, must be used to justify certain design decisions (Spielvogel, 1978; Woods *et al.*, 1978; Schipper, 1976). Examples of the use of life-cycle-costing include: (i) decisions regarding the cost effectiveness of proposed energy conservation measures; (ii) justification for passive and active solar energy systems; (iii) selection among alternative environmental control systems, such as combustion heating or heat pump systems; (iv) optimization of hybrid systems consiting of passive and active solar energy systems which assist conventional systems.

To successfully incorporate life-cycle-cost analysis into the decision-making process for building design requires a certain amount of change from conventional practice. For example, the financing of new construction based on life-cycle-costs requires that factors other than low first costs be considered. This approach also implies that the dynamic performance of building systems can be adequately predicted. Thus, while there have been changes in economic evaluation over the last six years, it must be recognized that these economic concepts are basically new to the building industry.

CONCLUSIONS

During the last six years, architectural and urban biometeorology has seen a profound change. New concepts and directions have been identified which should influence the future of this discipline for many years. The rapid development of these new design criteria has also identified many new areas in research that must be pursued. Our challenge in the decade ahead will be to provide designs which are responsive to the needs of the occupants, but which are also responsive to the constraints which must be imposed i.e. costs, environment, natural resources, health, and safety.

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Pollution, Biomagnetism, EM Fields, Light, Noise, Atmospheric Pressure Fluctuations, High Altitude Effects

Biological Effects of Chemical Pollutants

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Compared with our review published in 1974* there has been moderate growth in epidemiological data, but the data generation in experimental settings was considerable. *In vitro* experiments with cell cultures are now widely used to study working mechanisms of environmental pollutants on living cells, using their biochemical parameters, especially enzymes.

Testing for mutagenicity using, for example, the Ames test (Ames *et al.*, 1973) amongst others, offers possibilities to screen large numbers of chemicals for potential mutagenic or carcinogenic effects. Compared with animal experimentation, this offers a chance to save money and time. There is some doubt however as to whether the systems now in use are not producing some false positive or false negative effects when extrapolating to the human situation (Int. Agency Res. on Cancer, 1977). There is also the problem of dose-effect and dose response extrapolation.

At last it is dawning that we are in fact being confronted with an increasing number of new chemicals each year and the need for a simple screening system is evident. Both the US (TOSCA or Toxic Substances Control Act) and the EEC are beginning to request a considerable amount of toxicological data on a new chemical before it can be admitted to the market.

The set of *air quality criteria* documents, initiated by the United States Public Health Service, was never completed and remained restricted to SO_2, particulates, CO, NO_2 and O_3. WHO (World Health Organization) published, in 1972, an urban air quality criteria document for the same set of pollutants. This report gained wide recognition for public health protection. Table 1 gives the long term goals recommended by the WHO report. Biersteker (1976) and Ellison and

*Biological effects of clinical pollutants. In *Progress in Human Biometeorolgy,* Part 1A, (ed. S.W. Tromp) 1974, pp. 89–98.

Waller (1978) published updated reviews of the health effect studies dealing with SO_2 and particulates. The main conclusion of both reviews was that air pollution criteria documents still have to use old data, mainly gathered in Great Britain, to formulate air quality goals. Attempts in the USA to rewrite their air quality criteria documents also failed for lack of new data. Ferris (1978) published a review, which was then discussed at the meeting of the Air Pollution Control Association at its 71st Annual Meeting in Houston by a panel of experts. Though the weaknesses of some of the older and more recent studies were stressed, no practical proposals for change of the US federal standards resulted from the meeting.

Table 1. Recommended long-term goals

Pollutant and measurement method		Limiting level
Sulfur oxides[a] – British Standard Procedure[b]	annual mean 98 % of observations[c] below	60 $\mu g/m^3$ 200 $\mu g/m^3$
Suspended particulates[a] – British Standard Procedure[b]	annual mean 98 % of observations[c] below	40 $\mu g/m^3$ 120 $\mu g/m^3$
Carbon monoxide – nondispersive infrared[b]	8-h average 1-h maximum	10 mg/m^3 40 mg/m^3
Photochemical – oxidant as measured by neutral buffered KI method expressed as ozone	8-h average 1-h maximum	60 $\mu g/m^3$ 120 $\mu g/m^3$

[a]Values for sulfur oxides and suspended particulates apply only in conjuction with one another.
[b]Methods are not those necessarily recommended but indicate those on which these units have been based. Where other methods are used an appropriate adjustment may be necessary.
[c]The permissible 2 % of observations over this limit may not fall on consecutive days.

Though the USSR has over a hundred ambient air standards (Biersteker, 1976), the criteria documents are often difficult to consult. In many cases physiological responses of doubtful public health significance play a role in setting such standards. Setting standards for carcinogens has proved to be a difficult problem, as there is doubt about a zero-effect level. In any case, it will be very difficult to use epidemiological studies to prove a zero-effect level in case of non-specific tumors like lung cancer, stomach cancer, etc. The only definite causal relationships in fact have been found for specific tumors (e.g.

angiosarcoma is caused by vinylchloride, mesothelioma is caused by asbestos fibres).

Since the appearance of the W H O technical report 506 (1972), which dealth with the urban air pollutants SO_2, smoke, CO, NO_2 and O_3, there has been very little new data acquisition in air pollution epidemiology. The CHESS program in the USA came with the conclusion that sulphates might play an important role in explaining some of the health effects. The sulphate concentrations were in general very low however, rarely more than $15 \mu g/m^3$ and experimental work by Amdur, Bayles and Underhill (1978) throws doubt on this conclusion. According to Amdur the term suspended sulphate is toxicologically meaningless. Table 2 gives the irritant potency of sulphate aerosols in the submicrometer range for guinea pigs. She stresses the importance of metal salts in studies of urban air pollutants which try to unravel the complexities.

Table 2. Relative irritant potency of sulphates

Sulphuric acid	100
Zinc ammonium sulphate	33
Ferric sulphate	26
Zinc sulphate	19
Ammonium sulphate	10
Ammonium bisulphate	3
Cupric sulphate	2
Ferrous sulphate	0.7
Sodium sulphate	0.7
Manganous sulphate	−0.9[a]

[a] Resistance decreased; change was not significant.

The complexity of the defense mechanisms of the human lung is increased by the large number of different types of cell involved. There are at least a dozen of cell types with phagocytic, immunological and allergenic activities (Kilburn, 1976). The general consensus is that air pollution plays a primary as well as a secondary role in the biochemical processes that may lead to *asthma, emphysema,* reduced resistance to *viral* or *bacterial infections,* and *autolytical* reactions. Considering the mainly unknown role of genetic predisposition, air pollution is an additional burden for both old and young persons in most communities, though our understanding in detail of the mechanisms per individual is still very poor.

As for the carcinogenic action of NO_2, O_3 and SO_2 in ambient air, epidemiological proof is yet to be uncovered (Von Nieding, 1978). There are indications, however, that lung cancer, produced in test animals, is enhanced when benzo(*a*)pyrene is combined with SO_2 and NO_2 (Laskin *et al.* 1976). There is a consensus that in real life cocarcinogens and promoting agents play a contributory role in the epidemiology of lung cancer. The urban rural difference in lung cancer death rates in Great Britain are much smaller now than 10 years ago (Lawther and Waller, 1978). Even so, there is room for the hypothesis that at least in the past air pollution other than smoking contributed to these differences. According to the International Symposium on General Air Pollution and Human Health (1977), with special reference to long-term effects, there is need for further studies to elucidate the responsible factors.

In the meantime WHO started a new series of environmental health criteria documents. Reports on oxides of nitrogen, photochemical oxidants, sulphur oxides and suspended particulate matter appeared as numbers 4, 7 and 8 in this series. Interested readers can find up-dated reviews of the relevant literature on these pollutants in these documents. Documents on lead and carbon monoxide are also available from WHO.

As for the effects of specific industrial pollutants (Biersteker, 1975), the Seveso incident with TCDD gained worldwide notice as an example of possible risks involved with the manufacturing of toxic chemicals (Bonaccorsi, Fanelli and Togoni, 1978).

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Studies (1973–1978) on the Biological Effects of Low and Extremely Low Frequency Electromagnetic Fields

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When presented with an apparently insoluble and complex methodological problem, a normal and predictable human behaviour is an all-or-nothing response: to reject the phenomenon totally or to accept it without question. Various forms of emotional behaviors, typically displayed in the midst of these phenomena, reduce even further the scientist's ability to discriminate the essential stimulus operations and to evaluate objective changes. Such counterproductive behaviors, antagonized by recent political, popular and psychological factors, have complicated essential research of extremely low frequency (ELF) electromagnetic (EM) field effects. Any review of work generated during 1973–1978 must be evaluated carefully according to precise methodology and absolute changes rather than general conclusions such as 'effect or no effect'.

The ELF label has been used to designate electromagnetic field-waves of 10 Hz ± 1 kHz (0.01 Hz–10 kHz) or pulses within this range from higher frequency waves (Persinger, Ludwig and Ossenkopp, 1973). Traditionally, general biometeorological interest in these particular EM phenomena reflected their: (1) occurrence during various geophysical-meteorological conditions, (2) unusual penetrability and propagation properties, and (3) similarity to EM patterns generated by living systems including man.

Biometeorological-relevant ELF research before 1973 (Persinger, 1974) displayed a rich variety of experimental frequencies, intensities (1 nT–100 mT and 1 mV/m–100 V/m) and wave forms. Unfortunately,

Editor's Note: A summary of the major studies on biological effects of EM fields during the period 1963–1970 was given by Reiter. In *Progress in Human Biometeorology* Part IA. (ed. S.W. Tromp) Swets & Zeitlinger Publ. Co., Amsterdam/Lisse, 1974, 32–33 and 329–334.

within the rich variety, there is little reliable substance. Most of the experiments (i) did not specify elementary (and essential) methodological details, (ii) utilized gross or multiconfounded measurements and (iii) generally appear as fragments of singular hypothesis testing rather than a systematic approach. The field is still kaleidoscopic.

In the last six years, the texture of ELF research has been influenced notably by three main factors: First social concerns, specifically the US Navy's Project Sanguine (Seafarer) and ELF-EM generating 10 000 km^2 grid system, and potential deleterious consequences of high voltage 60 Hz power lines; second, the use of operant behavioral methods of measurement; and third, a renewed interest in 'electromagnetic medicine' for treatment of specific human disorders. Several episodes of media-induced paranoia associated with alleged untoward effects from ELF pulses of MHz signals generated by other countries were evoked in the USA and Canada by individuals not conversant with the scientific literature.

Ten reviews or general articles concerned primarily with pulsed ELF signals or high power sources have been published during this period (e.g. Bridges, 1978; Marino and Becker, 1977; Milroy, O'Grady and Prince, 1974). The most negative summary of ELF-EM effects was the Report of the Committee of 'Biosphere Effects of Extremely-Low-Frequency Radiation', published by the National Academy of Sciences (1977) pursuant to a contract with the US Navy. Allegedly a critical summary of the present status of ELF work, the document contains an extraordinary bias: if a single study did not find any ELF effect, then there is no effect; if a single study did report an ELF effect, then there is no effect.

Three general data patterns have emerged from the ELF literature. The effects of near-natural intensities (nT–μT) or supranatural intensities (μT–10 mT) upon normal adult animals are (i) very small, if present, (ii) can be masked easily by many routine experimental procedures, and (iii) comparable in magnitude to a multitude of background stimuli. For example, research in this laboratory indicated clearly that 5-day exposures of 40 adult male rats to 0.5 Hz magnetic fields between 10 nT and 1 μT variation did not influence significantly: (i) any of 20 different blood measures determined automatically by computer (Persinger *et al.*, 1978a), and (ii) circulating blood T3 and thyroxine levels or thyroid follicle and mast cell numbers (Lafrenière and Persinger, 1978). Similarly, 48 adult female rats exposed for 10 days to 0.5 Hz variations between 0.1 μT and 1 mT displayed no discernible changes in thyroid morphology or other tissue wet weights (Persinger, Lafrenière and Carrey, 1978b). Significant interactions between pre-exposure housing conditions and ELF-EM field intensities were evident for serum glutamate oxaloacetic transaminase activity and for thyroid and spleen weights in these studies.

A continuation of this pattern has been noted in human and non-human behavioral measurements recorded during acute (short-term) ELF exposures. In fact, the earlier reports by König (1971) and by Hamer (1968), who reported significant changes in reaction time (RT) during 2–12 Hz, 1–4 V/m field presentations, have not been replicated clearly by other experimenters. Persinger, Lafrenière and Mainprize (1975) exposed 70 male and female human subjects during 40 min sessions to successive 10 min presentations of either 3 Hz or 10 Hz electric fields of 3.0 V/m, 0.3 V/m or sham conditions. No statistically significant differences in mean RT were associated with any of the field conditions; in fact, 99 % of the variance in mean RTs could be explained by: (i) duration within the experimental paradigm, (ii) individual differences, (iii) sex differences and (iv) RT stimulus (a light) presentation pattern. The last three factors plus field condition did contribute to the standard deviation of RTs in a small but significant manner.

As aptly stated by de Lorge many times, the more controlled the behavioral paradigm, the less likely any ELF-associated effects are observed. There is a clear difference between the earlier anecdotal experiments used to prove personal hypotheses and systematic research, as de Lorge's research demonstrates. In a series of well designed and executed experiments involving monkeys, rats and pigeons exposed for periods of hours up to days to a variety of ELF frequencies (7–75 Hz) and intensities (0.1–10 mT; 1–30 V/m), de Lorge and his colleagues (de Lorge and Grissett, 1977) have found no reliable change in the several operant measures employed.

Although normal adult mammals have not responded systematically to experimental ELF-EM fields, some aquatic or avian species have displayed reliable effects. The motility of protozoa (Friend, Finch and Schwan, 1975) and the mitosis of microplasmodia from slime mold (Goodman, Greenbaum and Marron, 1976) have shown alterations during applications of ELF fields around 1 V/m and 0.1 mT. Several experiments by Southern (1975) and Larkin and Keeton (1976) strongly indicate that ELF-EM fields affect bird orienting responses. Whether these changes reflect real species differences or methodological approaches has not been evaluated.

The second general pattern of ELF data originates from experiments involved with field parameters far exceeding typical meteorgenic ELF values or forms, specifically: (i) 50 or 60 Hz fields comparable to energy values of several kV/m, and (ii) energetic microwave or radio-frequencies pulsed within ELF ranges. The majority of well-designed high voltage experiments in the USA have been reported by Marino and Becker and their colleagues (Marino *et al.*, 1977). Their studies indicate that long-term exposure of mice to 60 Hz fields of 150 V/cm induced alterations in body weight and several blood measures characteristic of general 'stressors'.

The microwave-pulsing approach is typified by the experiments of Adey and colleagues (Bawin, Gavalas-Medici and Adey, 1973) who found that 147 MHz, 1.0 mW/cm^2 fields, amplitude modulated at 0.5–30 Hz (ELF pulses) elicited obvious post-exposure electroencephalographic changes in cats. Although both lines of research offer exciting challenges to the general problems of electromagnetic noise in the twenty-first century, and, especially the unspecified complications of microwave power applied in ELF pulses to the nervous system, they are secondary to the scope of classical biometeorology. Synergisms between man-made EM noise and geophysical-meteorological ELF fields are a theoretical necessity; their practical demonstration is an empirical nightmare.

A renewed interest in 'electromagnetic medicine', a concept that has been entertained and discarded several times within western culture, comprises the third data pattern. The implicit assumptions of most magnetotherapies is that EM fields normalize or reduce symptoms of low-level heterostasis, typical of those paired to weather changes. General discussions of this concept have been published by Ludwig (1977) and Von Warnke (1978).

Space does not permit proper evaluation of the many laboratories in Europe, Asia and North America involved with some form of weather-related ELF magnetotherapies. One of the more serious series of experiments has been conducted by Ludwig and his colleagues. Displaying a rare integration of theoretical conception, technical development and experimental testing, Ludwig has: (i) used special electromagnetic screening to evaluate the contribution of ambient atmospherics to arthritic complaints (Ludwig, 1973), (ii) developed portable, pocket-sized ELF generators to allow greater mobility of experimental subjects, and (iii) tested the therapeutic value of weather-like ELF pulses (Ehrmann *et al.*, 1976). Although Ludwig and his medical colleagues appear conversant with placebo problems and utilized blind controls in their procedures, the extraordinary sensitivity of the symptoms most influenced by magnetotherapy of a multitude of non-verbal cues must temper generalization at this time. Replication of these effects in several different laboratories, preferably by experimenters negative to ELF magnetotherapy is essential.

The introduction of one final major concept – pharmacological enhancement – could change the probationary status of ELF fields as biometeorologically relevant stimuli. This operation assumes that some optimal drug treatment to living systems before or during the presentation of elsewise ineffective ELF fields, will enhance negligible organismic alterations to large and replicable magnitudes. Until this phenomenon is demonstrated, however, ELF-EM effects in biometeorology must remain within the vast heterogenous pool of low-level background stimuli that occasionally emerge from the normal variability of biobehavioral measurements.

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Observations on the Physiological Effects of Reduced Light Stimulation in Man*

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INTRODUCTION

In *Progress in Human Biometeorology*, Part IA, pp. 373–377 (Tromp, 1974) a summary was given by the authors of the physiological effects observed in man till 1970, due to reduced light stimulation of the eye. In the same series Part II: pp. 49–50 (Tromp, 1977) a brief compilation was given of the effects of reduced light on rhythmic excretion of urinary substances. In the present paper the authors summarized the principal studies carried out after 1970 with blind subjects, particularly during the period 1973–1978.

CLINICAL OBSERVATIONS

Human blood studies

Hollwich and Dieckhues (1973) studies the daily changes in blood composition in 40 blind and 25 normal subjects. The pronounced daily rhythmic changes in total leucocytes, neutrophils, lymphocytes and reticulocytes and of the haematocrit values almost disappeared in the case of blind subjects. In some instances even an reverse relationship developed in blind subjects.

The usual increase during the morning of total leucocytes and lymphocytes and the decrease of eosinophils in normal subjects was missing in 300 observed blind subjects. The average daily curves in blind subjects are considerably lower than in normal subjects. Also the pronounced daily fluctuations of thrombocytes in normal subjects were disturbed in 250 observed blind subjects. Normally a minimum

*English summary of the original German paper of F. Hollwich and B. Dieckhues prepared by the editor, S.W. Tromp.

occurs between 11.00 and 12.00 h and a maximum around 20.00 h. In blind subjects only a small minimum occurs around 20.00 h, the amplitude is lowered and the total number of thrombocytes is reduced.

Metabolic studies

In 1974 Hollwich and Dieckhues examined 100 blind and 50 normal subjects. Every 3 h uric acid, creatinin, urea-N, bilirubin, sodium, potassium, calcium, chloride, inorganic phosphate, 17-ketosteroids and 17-OH-corticosteroids were analysed in urinary samples. As compared with normal subjects, in blind subjects the following observations were made: (1) disturbance in the excretion rhythm (desynchronization and lowering of the rhythm amplitude) and (2) disturbance of the total excretion (which was reduced).

Former studies on liver metabolism in animals by Hollwich and Dieckhues in 1966 have shown the difference in lethality of nembutal if applied to mice kept in the dark or in light. Lethality is greater in rats kept in the dark because the breakdown in the liver into non-toxic substances in slowed down in a dark environment. On the other hand the lethality of nitrostigmin (E-605) is greater in mice kept in a lighted environment. Due to the light stimuli the liver metabolism transforms the non-toxic nitrostigmin (E-605) in the toxic, cholinesterase inhibiting, substance mintacol.

Similar observations were made in humans by determining the serum bilirubin level in 400 blind and 80 normal subjects. The bilirubin level was significantly higher in blind subjects due to a reduced breakdown of bilirubin in the liver.

Hormonal studies

Several studies were carried out by Dieckhues in 1974 and by Hollwich and Dieckhues in 1977. With radioimmunological methods the fluctuations in blood of adrenocorticotrophic hormone (ACTH), cortisol, growth hormone, follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, thyroid-stimulating hormone (TSH), triiodothyronine (T3-test), thyroxine (T4-test) and insulin were analysed. Also the urinary excretion of catecholamines, gonadotropins and vanillin-mandelic acid were studied. In 60 blind, as compared with 25 normal subjects, a significant reduction was observed in the excretion of ACTH, cortisol, growth hormone, thyroxine, gonadotropin, catecholamines and vanillin-mandelic acids. Also the amplitudes of the fluctuations were smaller. TSH, insulin and thyroxine were not significantly reduced.

Also genital activity changes were studied by analyzing changes in testosterone and LH secretion. In 34 blind and 50 normal subjects in the same age groups a significant reduction in testosterone and LH secretion was observed in the blind subjects (Lenau *et al.*, 1967).

In 1977 Hollwich, Dieckhues and Schrameyer studied the differences in daily secretion cycles of blind subjects with different degree of light perception: 10 totally blind, 5 subjects with some light perception and 5 with good light perception without, however, the ability to recognize objects. Fluctuations in secretion of ACTH, cortisol, growth-hormone, testosterone, TSH, thyronine and thyroxine were determined. Subjects with no light perception at all had the lowest secretion values of these different hormones, particularly at 08.00 h.

With increasing light sensitivity the values increased and approach in the third group the average values observed in normal subjects. This suggests that the hormone secretion in humans and their metabolic processes are greatly dependent on the degree of light stimulation in their environment.

Bodenheimer *et al.* (1973) in seven, and D. Alessandro *et al.* (1974) in ten blind subjects observed similar phenomena in their plasma cortisol secretion.

Studies with cataract patients confirmed that these hormonal and metabolic changes are entirely photoperiodic effects. Measurements of the same subjects before and after a successful cataract operation (leading to normal light perception), whereas thermal and other environmental conditions remained the same in both cases, indicate that only a change in light perception was responsible for these hormonal changes. Additional control experiments clearly demonstrated that operative and postoperative stresses were not responsible for these changes (Hollwich and Dieckhues, 1977b).

The effect of light stimuli on the human eye can be demonstrated not only in blinds, with different degree of light perception, or cataract patients, but also in normal subjects by increasing the artificial light intensity near their eyes. Hollwich, Dieckhues and Meiners (1975) could demonstrate increased hormonal and metabolic functions after increased lighting. From a practical point it is also important that the same research workers observed different results with natural and artificial light. The danger of covering all school windows in Canada and Sweden, as a protection against a cold environment, propagated in certain circles in these countries, is clearly demonstrated by further studies by Hollwich, Dieckhues and Schrameyer (1977) in the 'Experimental Station for Biological Light Effect Studies' at the University Eye Clinic at Münster (W. Germany). The application of artificial light for long periods increases the metabolic processes to such an extent that stress conditions are created by overstimulating the hormone producing centres in the body.

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Observations on the Endocrinological Effects of Light

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INTRODUCTION

In recent years numerous publications have appeared on the effects of light upon some parts of the neuroendocrine system in animals and in man. The studies have been mainly carried out from a physiological point of view, unlike previous studies of the effects of light upon the morphological and histophysiological characteristics of this system. The results of these studies on the role of light in the determination of the circadian and seasonal rhythm of the endocrine system, represent a morphophysiological base for evaluation of the impact of light as an environmental factor of great importance in the regulation of numerous adaptational processes of the organism.

With regard to the knowledge of the eye as a photoreceptive organ, recent publications testify to the existence of the direct retino-hypothalamic projections of the nerve terminals of the retinal origin, in the preoptic area in *Rana temporaria* (Vullings and Heussen, 1975), in the suprachiasmatic nucleus of birds (Benoit and Assenmacher, 1973; Bons, 1974, 1976; Hartwig, 1974) and in mammals (Printz and Hall, 1974; Moore, 1974; Thorpe, 1975; Sawaki, 1977).

The hypothalamo-hypophysial complex represents a strategic area in the determination of the effects of light upon the neuroendocrine system.

EFFECTS ON THE HYPOTHALAMUS

The suprachiasmatic nucleus and the superior cervical ganglion are involved in the neural regulation of the biorhythm of rats (Binkley and Geller, 1975). The hypothalamus seems to be the major photoreceptor (Oishi and Lauber, 1973a). Under the influence of long diurnal photoperiods, the suprachiasmatic nucleus is inhibited (Rusak and

Morin, 1976). In the preoptic nucleus of blinded frogs exposed to a long diurnal photoperiod or continuous darkness, there was no change in the amount of incorporated ^{35}S-cysteine, nor in the amount of the neurosecretory material, nor in the volume of the nuclei of the neuroglandular cells (Vullings, 1973). The uptake of serotonin by the suprachiasmatic nuclei is significantly higher in rats exposed to the influence of continuous darkness, but without significant differences under the effect of continuous light (Meyer and Quay, 1976). The changes in the retinal illumination can affect the electrical activity of the suprachiasmatic nuclei (Lincoln, Church and Mason, 1975); however, changes in a photoperiod do not influence the hypothalamic monoamine oxidase (MAO) in rats (Urry and Ellis, 1975). Electroencephalogram waves in the chicken hypothalamus are characterized by a flickering frequency (Shimada *et al.*, 1973). It is supposed that the infundibular nucleus plays a role in the determination of the hypothalamic control of the testis activity (Wilson, 1973).

EFFECTS ON THE HYPOPHYSIS

Light stimulates the somatotropic function of the hypophysis (Disclos, 1973). Under the influence of light, 16 h day, the growth rate of sheep is significantly faster than that of animals exposed to light periods of only 8 h day (Forbes *et al.*, 1975). It is assumed that the pineal gland plays a role in the determination of the speeded growth under the effect of daylight (Forbes, 1975). The FSH secretion increases in rats constantly exposed to light (Fink, 1975). The exposure to a non-stimulatory photoperiod does not alter the increased hypophysial FSH and LH content observed after castration (Turek *et al.*, 1975). Sheep kept in light 16 h day have higher plasma prolactin levels than those kept in light for 8 h (Forbes *et al.*, 1975). Under the effect of light, the secretion of ACTH, lipotropic hormone, and melanocyte stimulating hormone (MSH) occurs in the ferret (Hammond, 1973). The concentration of Na^+, K^+ and Mg^{2+} in the adenohypophysis is low during the day and increases during the night (Piechowiak and Schnizer, 1976). The pituitary monoamine oxidase activity is increased by constant light and by pinealectomy, and reduced by constant darkness as by application of melatonin (Urry *et al.*, 1975). The preovulatory release of LH in rats kept under the influence of continuous light, depends upon the release of a large amount of lutenising hormone-releasing factor (LH-RF) into the hypophysial portal system (Fink, 1975). Under the effect of light, a significantly higher sodium concentration in the neurohypophysis occurs (Piechowiak *et al.*, 1976).

EFFECTS ON THE THYROID GLAND

Under the influence of repetitive photostimulation in the chicken, the blood $PB^{131}I$ level is increased (Shimada *et al.*, 1973). Under the influence of continuous illumination in hibernal larvae (*Alytes obstetricans*), an acceleration of the morphogenetic evolution, the precocious metamorphosis, was noticed. Light participates in the regulation of morphogenesis by preventing the teratogenic activity of large doses of thyroxine (Disclos, 1973). The intensity and frequency of endemic goitre are especially manifested in areas with narrow valleys and little sunshine (Popescu, Postelnicu and Marcu, 1973).

EFFECTS ON THE PARATHYROID GLAND

The parathyroid gland undergoes cyclical seasonal structural changes. The seasonal variations in serum calcium levels are manifested in frogs; a factor derived from the hypophysis is involved in the determination of the histophysiological behaviour of the amphibian parathyroid gland (Daugherty, 1973).

EFFECTS ON THE ADRENAL GLAND

In man, and in animals with diurnal activities, the secretion of corticosteroids is increased over the night and decreased over the day; in nocturnal animals this rhythm is reversed (Assenmacher, 1973). In man, isolated deeply underground, without daylight for 3–6 months, the circadian rhythm in the function of the adrenal gland is preserved (Halberg, 1973). In studies on the role of the human eye in the maintenance of the circadian rhythm of the hypophysial-adrenal axis, the age of blinding is important; Wilson (1973) states that 'the eyes are necessary for synchronization with light-dark cycles but not for this rhythmicity *per se*'.

The persistence of the daily rhythm of Na^+, K-ATPase and glucose-6-phosphatase is observed in rats exposed to continuous light and to continuous darkness (Margolis, 1977). In male rats, the adrenal medullary dopamine-β-hydoxylase activity is increased approximately 6-fold under the influence of daylight than in the darkness (Banerji and Quay, 1976).

EFFECTS ON THE PINEAL GLAND

Antigonadotropic influence of the pineal gland is variously manifested in different seasons (Reiter, 1973). Atrophic changes are manifested in the gonads and their adnexa in female hamster under the influence of short daily photoperiods (Reiter, 1974). After bilateral removal of the cervical symphatetic chain, there are no changes in the reproductive organs of the female rat exposed to the effect of continuous light, nor in operated and sham-operated animals. The pineal gland is involved in mediating the effects of daylight on the growth of the sheep (Forbes, 1975), and implicated as a mediator of the effects of light upon reproduction (Hoffmann and Cullin, 1975). The pineal gland of the frog *Rana catesbiana* and *R. esculenta* responds very rapidly to light (Morita *et al.*, 1975). During the effect of long daily photoperiods, the pineal gland is not activated (Rusak *et al.*, 1976). In the early post-natal period, the photoperiod has a little direct effect on the development of the pineal parenchymal cells (Trakulrungsi and Yeager, 1977).

The circadian variations in the levels of the enzymes involved in the melatonin synthesis are under the influence of illumination; the rate of the norepinephrine release from the intrapineal symphatetic fibres is reduced (Zatz, 1975). Under the influence of an alternating light-dark photoperiod in the chicken, serum melatonin is not detectable during the light phase (Pelham, 1975). The daily rhythm of *N*-acetyltransferase activity in the chicken pineal gland is persistent in constant darkness (Binkley *et al.*, 1975). The levels of hydroxyindole-*O*-methyltransferase (HIOMT) are elevated in blinded guinea pigs (Faris and Botz, 1975). The same enzyme rises rapidly under the influence of constant illumination (Wainwright, 1975). The monoamine oxidase activity of the pineal gland is not influenced by constant illumination after birth (Illnerova, 1975). The lethality of mice under the influence of alloxan that were exposed to continuous light is notably higher than in continuous darkness (Nanu *et al.*, 1976). The synthesis and release of arginine vasotocin are enhanced during the night (Calb, Goldstein and Pavel, 1977). The circadian rhythm of serotonin in the pineal gland of the lizard is maintained under the constant effect of darkness and disappears under the influence of continuous illumination (Petit and Vivien-Roels, 1977).

EFFECTS ON THE OVARY

In studying the fish migration one must take into account the existence of the 'sun-compass', especially in the period from sunrise to sunset (Schwassmann, 1973). Under the influence of the early constant lighting, the female rat is less sensitive to light and more sensitive to darkness (Hoffmann, 1973b). After 12-week illumination, in sexually mature rats, the ovaries are polycystic and anovulatory; hyperandrogenism is manifested; the findings are similar to those obtained in Stein-Leventhal's syndrome in clinical treatment (Manguelle-Dicoum *et al.*, 1975). In long-term ovariectomized rats, there is no rise in the blood LH during the afternoon or evening hours in comparison with the morning values (Blask, 1974). Preovulatory surge of LH and ovulation are under the control of an endogenous circadian rhythm (McCormack and Sridaran, 1978). The disturbance of the menstrual cycle is more frequent in blind women; they usually suffer from amenorrhoea during the first months, the first year, and even longer, due to lack of light stimulation, i.e. correlative secretion of the sufficient quantities of FSH and LH (Schumann, 1973). The pineal gland is involved in the gonadal development and ovoposition in the fish (Urasaki, 1973).

EFFECTS ON THE TESTIS

In intact birds both red and green light are effective at low intensity (Oishi and Lauber, 1973b). Increased gonadotrophin secretion and testicular metamorphosis are observed in starlings exposed to a prolonged daily period of darkness (Schwab and Rutledge, 1978). Long photoperiods are not favourable for the reproduction of domestic animals; under the effect of light, the retroaction of steroids on the hypothalamo-hypophysial complex takes place (Ortavant, 1973). The annual testicular cycle in the hamster is not dependent on the absolute amount of light or darkness, but primarily on the position of light relative to the circadian system (Stetson, Elliott and Menaker, 1975). Continuous illumination has very little effect on the testis in the rat; in older rats, the plasma level of LH is increased (Hoffman, 1973a). Under the influence of the constant light and of the crowding, the testicular MAO activity is decreased (Frehn *et al.*, 1973). Diurnal variations of ascorbic acid and of cholesterol in the testis are observed; pinealectomy has a reverse effect on testicular cholesterol levels during the period of darkness (Damian, Janes, and Badescu, 1977).

DISCUSSION

The results of the studies of the endocrinological effects of light point to the importance of the photoperiod as a factor regulating the occurrence and maintenance of the circadian and seasonal rhythm of the neuroendocrine system. When taking these results into consideration, it is necessary to point out that in experimental conditions, in the different seasons, the physiological doses of light take their full physiological effect by either stimulatory or inhibitory actions in the chronology of the cyclic processes in some parts of the endocrine and neuroendocrine systems. Nonphysiological light doses, as well as the experimentally induced changes in the shift of light and darkness of unnatural duration, have quite a reverse effect. These doses provoke dissociation and disturbance in the functioning of some endocrine glands, that is to say, disturb the equilibrium of the neuroendocrine system. We are of the opinion that some results of the studies cited in this paper represent a reflection of the stress-inducing effect of light. Without going into a detailed analysis of the data on the role of the pineal gland in the determination of the effect of light, especially of the antistressogenic activity of the pineal gland (Miline, 1977), the results reviewed in this paper open new horizons in the study of the effect of light upon the neuroendocrine system, especially in the area of research embracing the regulation of the adaptational capabilities of the organism. Besides, one should always bear in mind that under normal living conditions – referring to animals as well as to man – the adaptation of the organism, or rather the correlative part of the organism belongs to some ecological and biometeorological factors (Klinker and Jordan, 1976).

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Effects of Noise on Blood Coagulation

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INTRODUCTION

The effect of noise stress on blood coagulation is unknown. It needs consideration in the light of increasing noise pollution as a result of the mushrooming of noisy industries, automobiles and aeroplanes vitiating the peaceful environments of habitation. A single or limited number of noise events may lead to annoyance and possibly do not constitute a major threat to homeostasis of the body in general, however, there is an increasing body of evidence that harmful noise stimuli affect a wide range of biochemical and physiological functions.

Noise exposure beyond 100 decibles (dB) promotes vasoconstriction in man (Jansen, 1964; Jansen and Rey, 1962; Lehmann and Tamm, 1956; Rosen, 1970). In rabbits and dogs, Strakhov (1964) found that noise stress of 100 dB or more over a duration of 6–152 days led to development of hypertension which persisted for several months after cessation of noise stimuli. The ECG showed pronounced increase in the ratio of the QRST interval to the R–R interval, indicative of impaired functional properties of cardiac muscle. During exposure to noise, there was marked lengthening of the P–Q segment of the ECG, lengthening of the QRS complex, and changes in wave forms, particularly R and T.* In dogs, there was a sharp strengthening of respiratory cardiac arrhythmia.

Shatolov, Saitanov and Glotov (1962) in Russia studied 300 workers regularly exposed to high frequency, 85–120 dB, industrial noise and reported abnormal ECG changes and hypertension. The ECG showed an abnormal falling off, levelling out and diphasic appearance of the T-wave. These observations were paralleled by corresponding ballistographic changes. In workers exposed to the higher noise levels of 114–120 dB these changes were more common and more extreme.

*Particularly R and T are suggestive of reduced intraventricular conductivity.

They reported that in human beings ECG showed bradycardia and a tendency to reduced intraventricular conductivity on exposure to noise.

Jerkova and Kremarova (1965) and Ponomarenko (1966) further confirmed the development of hypertension in individuals working in large engineering factories with constant high-frequency industrial noise.

Evidence exists that audiogenic stress induces, both in man and animals, hypertension accompanied with left ventricular hypertrophy (Selye, 1943; Buckley and Smookler, 1970; Rosecrans, Watzman and Buckley, 1966; McCann *et al.,* 1948; Medoff and Bongiovanni, 1945; Geber and Anderson, 1967).

Audiogenic stimulation, beyond a critical normal range, has been shown to induce increased cortico-adrenal activity in normal human beings (Arguelles *et al.,* 1962), and increased urinary catecholamines associated with raised levels of plasma cholesterol and 17-hydroxy-corticosteroids in individuals suffering from myocardial infarction and essential hypertension (Arguelles *et al.,* 1970). Highly significant elevation of plasma corticosteroids occur in patients suffering from anxiety after sound stimulation (Arguelles, 1967).

Lockett (1970) has shown that weight of adrenals and levels of urinary epinephrine increase in rats after intermittent exposure to noise. Histological evidence indicates sustained increases in hormone secretory activity in various zones of the adrenal cortex and the adrenal medulla in rabbits exposed to noise (Miline and Kochak, 1951).

The above observations prompted us to realize that these changes could not have been brought about without affecting the blood, blood vessels and the blood coagulation system. We have therefore carried out an experimental study in rats exposed to noise. The following paragraphs outline the changes in bleeding time, plasma fibrinogen levels and activated partial thromboplastin time on exposure to noise.

BLOOD COAGULATION CHANGES FOLLOWING NOISE EXPOSURE

Bleeding time, activated partial thromboplastin time (Biggs, 1976) and plasma fibrinogen concentration (Ratnoff and Menzie, 1951) were determined before and after noise exposure in four groups of female rats. The rats were 5–6 months old and average weight of 180 g. Each group comprised of 8 rats. The unexposed group acted as control. The test animals were exposed to a continuous noise of 110 dB for 2 h daily, 5 days in a week, over a period of three weeks. The noise was generated by a masking system of an audiometer and could be amplified to the desired level (Table 1).

Bleeding times, compared with those of controls (56.9 ± 5.2 s), were prolonged significantly in the group of test animals exposed to

Table 1. Blood coagulation parameters in rats before and after noise exposure (110 dB/2 h/day × 5/week) from one to three weeks.

Animals	Bleeding time (s)		APTT (s)		Plasma fibrinogen (mg/100 ml)	
	Mean	SEM	Mean	SEM	Mean	SEM
Controls (8)	56.9	5.19	15.6	1.01	116.7	6.48
One week exposed (8)	54.8	3.79	14.6	1.25	170.0	8.83[b]
Two week exposed (8)	56.2	8.88	–	–	141.6	14.77[a]
Three week exposed (8)	79.9	11.78[a]	13.9	1.08	177.5	6.99[b]
F-ratio	2.2279		0.6036		11.1780	

Parentheses indicate number of animals in each group. [a]$p < 0.05$, [b]$p < 0.001$.

noise for a period of 3 weeks. No significant change occurred in test animals exposed for 1 and 2 weeks.

Activated partial thromboplastin times showed a progressive shortening during the noise exposure and the change was most marked in the 3rd week in the test animals. Compared with controls (15.6 ± 1.01 s) the activated partial thromboplastin times were shorter in the test animals at the end of third week (13.9 ± 1.08 s), though the difference fell short of statistical significance.

Plasma fibrinogen concentration showed a steady and significant rise in test animals exposed for 1 and 3 weeks. Compared with the controls (116.7 ± 6.5 mg/100 ml plasma) the concentrations of fibrinogen were 170.0 ± 8.8 and 177.5 ± 6.9 mg/100 ml plasma at the end of 1 and 3 weeks respectively, however, the values of fibrinogen were 141.6 ± 14.8 mg/100 ml plasma in the test animals exposed for 2 weeks and this group showed a wide variation of fibrinogen levels ranging between 177 and 199 mg/100 ml of plasma (Rai, Singh and Chohan, 1979).

DISCUSSION

Prolonged bleeding time, shortened activated partial thromboplastin time, and raised plasma fibrinogen levels evidently result from exposure to obnoxious noise of 3 weeks duration in experimental animals. This triad complex suggests a coagulopathy and presents an extra-audiogenic effect of exposure to noise beyond a critical normal limit (Rai *et al.,* 1979). Shortening of activated partial thromboplastin time has been previously described in patients of disseminated intravascular coagulation (Williams *et al.,* 1972) and may reflect the presence of activated procoagulants in their plasma (Deykin, 1970).

The noise stress contributes to the 'Stress Syndrome' of Selye (1936; 1946; 1955) and influences the hypothalamo-hypophyseal-adrenal axis both in man and animals (Anderson *et al.*, 1965; Buckley *et al.*, 1970). The end result is mobilization of catecholamines. Catecholamines by favouring platelet aggregation (Born, 1968; Sutherland, 1965; Schwartz and Ardlie, 1962), stimulation of factor VIII synthesis (Cole, 1971; Brozovic, 1977), and activation of factor XII (McKay Latour and Parrish, 1970) promote coagulation on one hand but by enhancing fibrinolysis (Biggs, MacFarlane and Pilling, 1947) on the other hand tend to counteract it. Corticosteroids also promote fibrinolysis (Chakrabarty, Fearnley and Hocking, 1964). Under the noise stress both these mechanisms may operate but which process dominates probably depends on the intensity and duration of noise stress. Fibrinolytic response which may occur as a result of mobilization of catecholamines and corticosteroids by noise stimuli may not be adequate or may break down because of extreme severity of the stress, and thus predispose to coagulation process.

Increased plasma fibrinogen in the stressed animals provides abundant substrate for the blood clotting process. Increased levels of plasma fibrinogen and factor VIII are seen in large proportion of cases where intravascular coagulation forms a part of pathogenic process (Bowie *et al.*, 1972; Cooper, Bowie and Owen, 1974; Singh and Chohan, 1974). In our present study (Rai *et al.*, 1979) accelerated activated partial thromboplastin time and raised plasma fibrinogen suggest development of a hypercoagulable state as a result of noise exposure.

Noise induced coagulopathy may partly explain the pathophysiology of hypertension and adverse changes in the cardiovascular system in man and animals exposed to abnormally high frequency noise. The absence of this coagulopathy might have influenced the incidence of coronary heart disease and hypertension which is scarce in the noise free environments (Jansen *et al.*, 1964; Glorig, 1957; Glorig and Nixon, 1960; Rosen, 1970). The Mabaans tribe in Sudan, which lives in an atmosphere of virtual silence (35–40 dB) is free of coronary heart disease, hypertension and deafness, and enjoys longevity. However, when these members of the tribe are exposed to noisy urban environments they develop these disorders (Jansen *et al.*, 1964). The experience of Rosen (1970) among peasants of Yugoslavia and Crete is similar. Adverse effects of noise exposure such as rise in blood pressure (Buckley *et al.*, 1970), cardiovascular changes (Selye, 1943; Medoff *et al.*, 1945) and altered foetal cardiovascular response (Sontag, 1941; Geber, 1966; 1970) may, therefore, develop from changes in coagulation system. Further, Friedman, Byers and Brown (1967) have

Editor's note: It is interesting to note that a rise in fibrinogen content has been related to a rising diastolic blood pressure (Tromp, 1972).

produced evidence of higher blood cholesterol levels and presence of wide degree of aortic atherosclerosis in noise exposed rabbits. Recently Rai *et al.*, (1976) have reported increased levels of cholesterol, triglycerides and well adherence of platelets in human subjects exposed to gunfire noise (182 dB).

These adverse changes in blood coagulation, if confirmed in man, may predispose him to heart diseases. There is considerable evidence that exposure to higher level of noise has an adverse effect on the cardiovascular system. The results of our present study (Rai *et al.*, 1979) highlight the need for coagulation studies in human beings exposed to varied degrees of noise, a pollutant of universal importance and a grave threat to environmental health.

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Studies on Biomagnetic Responses of Living Organisms

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Barnothy (1974) gave an excellent review of the many studies on the biological effects of magnetic fields. On p. 394 she mentioned the observations by Pittman, between 1962 and 1970, on *geomagnetic tropism* of plants. Pittman observed already in 1962 that (Kharkov 22 m) winter wheat generally matures 4–6 days earlier when seeded in rows oriented North–South than when seeded in rows oriented East–West. Most plants had their visible roots orientated in a North–South direction. Later studies (Pittman and Woolley, 1966) using radioactive phosphorus, ^{32}P, indicated a greater root concentration in the soil on the North and South sides of the seed than elsewhere.

In 1970 Pittman and Omrod found that seeds of winter wheat (*Triticum aestivum L*), which were treated magnetically during 240 h with a field of 1800 gauss, at 23 °C before germination, respired more slowly, released less heat energy and grew faster during the initial 16 h than untreated seeds. The treated seeds absorbed more moisture and contained more reducing sugar during the initial 72 h of growth. Pittman explained this as a change in concentration or activity of auxins, hormones or enzymes due to the magnetic stimulus.

New studies by Pittman (1972) demonstrated also biomagnetic responses in potatoes. Plants grown in greenhouses from the excised, magnetically treated eyes of the Netted Gem Potato (*Solanum tuberosum L*) yielded a 38 % greater weight and 14 % more tubers than the untreated eyes.

More recent studies (Pittman, 1977) confirmed all these findings Preseedling magnetic treatment of barley seed (*Hordeum vulgare L*) or spring and winter wheat seed resulted in yield increases during 13–14 of the 20 tests.

Although the physiological processes in plants are entirely different from those in animals and man further studies may reveal similar biomagnetic phenomena both in animals and humans if treated for a long period with very strong magnetic fields.

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Possible Influence of Rapid Fluctuations in Atmospheric Pressure on Human Comfort

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INTRODUCTION

Rapid fluctuations of atmospheric pressure could be one of the few important physical variables responsible for the meteorotropic phenomena observed in weather sensitive humans. They claim to suffer from weather-induced discomfort regardless of whether they are in buildings or outside.

Some weather sensitive subjects claim that they experience a change in their well being before a change in the weather is observed (e.g. before foehn breaks in)*. If we are ready to accept these statements as facts, a variable which could cause discomfort must (a) be able to penetrate buildings, (b) be inert (it must not be changeable by man) and (c) have wave character in order to propagate from its source. Therefore, meteorological parameters e.g. humidity, windspeed, atmospheric temeprature, pressure, electrostatic fields, etc., which have important physiological effects, both inside buildings and outdoors, may not explain all meteorotropic phenomena observed in buildings.

In a recent study by Richner and Graber (1978) it was experimentally verified that only electromagnetic waves at very low frequencies and fluctuations of the atmospheric pressure with periods of several minutes, meet the requirements stated above. It must be realized, however, that the possible biological effects of electromagnetic or atmospheric pressure changes are weak compared with the above

*Editor's Note: As radio and press announce the approach of poor weather conditions, e.g. the foehn, etc., it is almost impossible to carry out an objective study excluding the psychological effects of a weather forecast. It is still doubtful whether certain humans can predict the approach of foehn weather before any changes of meteorological parameters can be recorded. Positive results have been obtained by the author with non-believers of weather effects and seem to be an exception to this rule (according to Richner).

important meteorological parameters. The same applies to reports suggesting ionic effects.

HISTORICAL DEVELOPMENTS OF RESEARCH

Much research on pressure fluctuations and their physiological effects was carried out in the first half of this century. Although some very valuable results have been obtained, pressure fluctuations as a biometeorological factor have disappeared completely from text books and research work is being published only very sparsely. It is therefore impossible to present a review paper at the present time. Instead, an attempt is made here to recall the early work in this field, to describe briefly the physics of atmospheric waves and, in a separate section, to present some general results of a research project carried out in the early seventies at the Laboratory for Atmospheric Physics ETH in Zürich, Switzerland.

After working on the physiological effects of foehn winds Ficker suspected that pressure fluctuations could cause discomfort. Measurements of such fluctuations under foehn conditions were carried out by Schmitt (1930) and Storm van Leeuwen and Booij (1933). Schmitt reported that mainly fluctuations with periods between 3 and 15 min had a negative influence on the well-being, Storm van Leeuwen and Booij found that pressure fluctuations with frequencies around 8 Hz—i.e. with periods around 0.125 s — were causing discomfort. Schmauss (1940) and Jordan (1940) also supported the hypothesis that well-being is affected by pressure fluctuations.

The results cited are not necessarily contradictory. Recent papers have shown that infrasound (frequencies 0.01—20 Hz) does cause discomfort (Evans, 1972; Hood, Leventhal and Kyriakides, 1972; Bryan, 1973). However, it cannot be plausibly explained how these frequencies could in general act as a carrier for weather induced discomfort since pressure fluctuations with a frequency of a few Hertz are highly damped when propagating. Booij (1937) concluded from the studies available at that time that infrasound is a very local phenomenon. Our own measurements fully confirm this result.

On the other hand slower pressure fluctuations with periods of several minutes are highly correlated with meteorological processes on a sub-synoptic scale. These fluctuations cannot be sensed by our ears as is the case for infrasound. Courvoisier (1949) has shown that these very low frequencies are broken up into higher ones by the subject's involuntary swallowing. He therefore concluded that Schmitt's (1930) results which showed a physiological effect of fluctuations in atmospheric pressure, with periods of several minutes, must be incorrect. This reasoning must be rejected since it is based on the assumption that pressure fluctuations can be sensed only by the ear. As will be shown later, there are further hypothetical mechanisms by which the organism could perceive very low frequency pressure fluctuations.

A statistical study by Richner (1977) has shown that gravity waves are present whenever there is an internal boundary layer, i.e. a surface of discontinuity in the atmosphere. This is the case under foehn conditions (warm foehn air moving over a pool of cold air) or when a front is present (boundary between the two air masses). It should be mentioned at this point that these two situations are those under which weather-sensitive persons seem to suffer most (see e.g. Brezowsky and Grimmeisen, 1967). Also, it is very important that, for example in the case of foehn, the increase in amplitude of the pressure fluctuations in the cold pool is the only indication of foehn above i.e. there is no change in any classical meteorological parameter before the foehn breaks in. Therefore, pressure fluctuations do have the necessary properties for transmitting information about the weather before the situation becomes apparent in classical terms on the ground (Fig. 1).

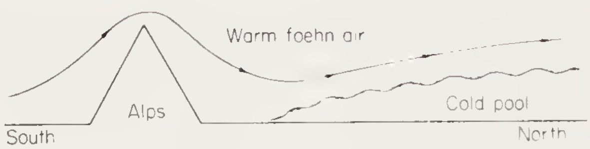

Fig. 1. South-North cross-section showing how a boundary surface between the foehn air and the cold pool is formed. Shear-induced gravity waves are generated at this surface.

The distinction between 'infrasound' (periods 0.05 s–3 min) and 'pressure fluctuations' (periods 4–30 min) can be physically justified. In fact it can be shown experimentally, as well as theoretically, that there is a gap in the frequency spectrum between these two ranges (Tolstoy, 1973). The propagation of infrasound is governed only by the compressibility of the atmosphere. Below the so-called acoustic cut-off frequency no propagation is possible. Propagation of pressure fluctuations is analog to the propagation of water waves. Here the fact that a gravitational field acts on a stratified atmosphere supplies the physical basis. For this reason these fluctuations are commonly called *gravity waves* in contrast to the *acoustic waves* described above. As mentioned above there is a distinct gap between these two frequency ranges. Gossard and Hooke (1975) have described the theory behind the complete range of atmospheric waves and have also collected and discussed a great number of research papers on this subject.

RESULTS FROM A STUDY IN ZÜRICH

The results which are presented here emerged from a carefully planned study carried out in the early seventies. The aim of the project was to either prove or disprove the hypothesis that pressure fluctuations are correlate with human comfort and ailments.

Method

On the physical side, mean amplitudes of acoustic pressure waves (periods shorter than ~4 min) and of gravity waves (periods longer than ~4 min) in 2-h intervals provided the meteorological set of data. These amplitudes were measured by a so-called microbarovariograph (Nater and Richner, 1977).

On the physiological side, the study was based on the evaluation of questionnaires filled in daily by 200 persons during a period of 7 months. The number of persons and the duration of the study assured that a statistically significant statement concerning the possible influence of pressure fluctuations could be made and that their action could be isolated from the action of hundreds of other parameters, which affected the well-being of the sample as well. Although, unfortunately, it was impossible to collect *objective* data from this large, healthy and normally working sample, the questionnaire was constructed such that the *subjective* well-being was obtained. In this way it was possible to obtain data which was free from any bias that the investigators may have held. The main part of the questionnaire used for recording the data contained two groups of questions: the first referred to ailments and could be answered with 'yes' or 'no' while the second consisted of pairs of antonyms (e.g. tired–fresh) separated by a straight line. The person questioned had to mark that point on the line which represented best his or her actual subjective feeling. Further questions dealt with the room climate and intake of medicine. About 25 000 questionnaires furnished 28 time series on the frequency of ailments and on the state of well-being. Data was reduced by creating two additional time series. The first – called sum of ailments – included the total frequency of ailments regardless of their type, the second – called index of well-being – represented a mean of all the scaled answers to the bipolar questions.

Results

The results can be summarized as follows:

No correlations were found between the amplitudes of pressure fluctuations with periods shorter than 4 min (i.e. acoustic waves) and biological data. However, correlations exist between pressure fluctuations with periods longer than 4 min (i.e. gravity waves) and the time series calculated from the questionnaires. Figure 2 shows an example of regression lines for the total sample (TT), for the group believing that weather has physiological effects (WF), and for the group not believing in this effect (NW). The horizontal axis shows the amplitude of the gravity waves in arbitrary pressure units, the vertical axis shows in the top part the index of well-being and in the bottom part the sum of ailments in percentages. The mean pressure amplitude is around 8.5 units, the amplitude near a front 17 units. The corresponding increase in the sum of ailments is 7% which equals a *relative* increase of roughly 20%. The coefficients of correlation are all rather low (0.3–0.4) since many other uncontrollable factors influence ailment and well-being. However, because of the length of the time series and the number of questionnaires the error probability is 0.1% for $r = 0.254$ and 1% for $r = 0.200$. For the index of well-being as well as for the sum of ailments the group WF showed a highly significant relation (0.1%). The group NW showed a significant 1% correlation in ailments but only a very probable significant (10%) correlation in their well-being. In other words: even the group NW is affected by weather induced ailments although their well-being is not significantly correlated with the weather (which in turn causes a bias, in their opinion, in the weather/physiology mechanism). As can be expected the difference between the correlation coefficients for the two groups WF and NW is highly significant.

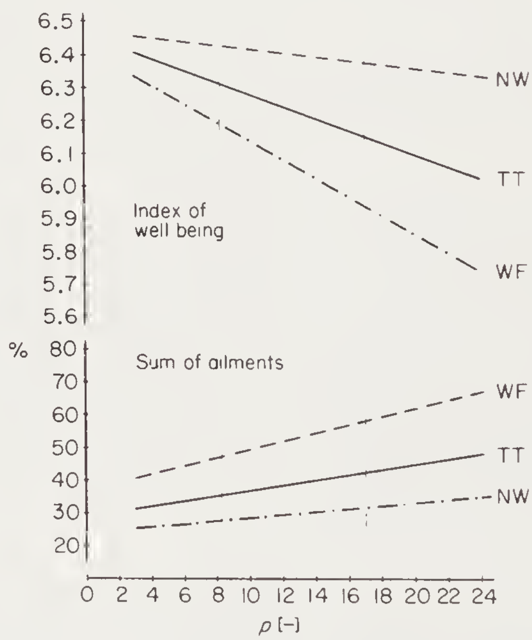

Fig. 2. Regression lines between the amplitude of pressure fluctuations and the index of well-being/sum of ailments for the total sample (TT), for the group believing that weather has physiological effects (WF), and for the group not believing in this effect (NW).

Similar calculations made for other groups, yielded correlations which are stronger for women than for men and stronger for people working in airconditioned rooms than for those working in non-air-conditioned rooms. The correlation coefficients were always positive and had an error probability of typically 0.1 %, never exceeding 1 %. The result concerning airconditioning is somewhat surprising. It led to a special study of pressure fluctuations in airconditioned buildings. It was found that also in these buildings atmospheric fluctuations are present and practically undamped if their period is not shorter than about 10 s. In addition there are several types of additional pressure fluctuations which are created by the airconditioning apparatus itself.

Surprisingly no correlation was found between the occurrence of headaches and pressure fluctuations for the group believing that their well-being depends on the weather. Headache was the most frequent ailment; although, in the mean 12 % of all the persons suffered from headache it seemed that it is not a typical weather induced disturbance.

An evaluation of the data according to age showed that people between 30 and 50 years of age tend to reveal stronger correlation between the pressure fluctuations and their subjective well-being and their ailments respectively.

Conclusion

Although research work early in the century led us to expect a connection between the amplitude of gravity pressure waves and well-being, our purely statistical study did in fact show a surprisingly strong correlation between these variables. However, it did not prove that atmospheric pressure fluctuations are the actual cause of ailments or aggravated well-being although this meteorological parameter has the necessary properties which would enable it to act as a direct biotropic factor.

Under the tentative assumption that pressure fluctuations are the direct cause of certain physiological disturbances a hypothetical mechanism of the physiological reaction was set up. The fact that no correlation was found between ailments and *acoustic* pressure waves indicates that the frequency of the physical disturbance plays an important role; this aspect was carefully considered in the following hypothesis.

It seems necessary that the human organism has some control system which enables it to adjust to large variations of the ambient pressure. The latter can be due to a changing pressure distribution around the globe or to the subject's travelling to different heights above sea level. The control mechanism – which presently is unknown – must have a certain time constant as every control loop does. If now the outer disturbance varies with a period about equal to twice the time constant of the control loop, the system becomes unstable.

On a tilting table an analogue mechanism can be demonstrated for the organism's control of blood pressure. There the instability leads to a collapse. For the hypothetical pressure control loop the reaction does not seem to be as severe but it could be coupled with general discomfort.

Editors note: Again it must be stressed that this hypothesis is based on the yet unproven theory that pressure fluctuations may represent an important cause of certain disturbances in human comfort, particularly in those cases where subjects live in buildings and where the usual meteorological parameters either cannot penetrate or do not vary very much. Under normal outdoor weather conditions the biological effects of atmospheric fluctuations are probably very small as compared with the thermal, radiation or altitude effects of the atmosphere.

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Effects of Mountain Climate in the Great Caucasus, the Pamirs and Tien-Shan on the Human and Animal Organism

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INTRODUCTION

A review of the data obtained in the USSR over the period 1973–1978 might begin with the words: 'Studies of previous years were continued'. However, there is no assurance that the previous results are well known to those interested in the subject. It seems reasonable, therefore, to give first a short review of the previous studies and to mention the scientific centres concerned with mountain physiology.

Effects of mountain climate in the Pamirs and Tien-Shan were studied mainly by the scientists of the Kirghiz, Tadjik and Kazakh National Republics. The scientists of the European part of the Soviet Union generally work in the Caucasus. Joint expeditions involving workers of European and Asiatic Institutes of the USSR have been organized and proved to be successful.

Practically all the Soviet researchers concerned with problems of mountain physiology and pathology were active participants in the 'Human Adaptability' Section within the framework of the International Biological Programme during 1967–1973. The results obtained from these studies were published in the Proceedings of many conferences, monographs and special books issued by the National IBP Committee, such as *Human Adaptability* (1972), *Man and Environment* (1975), *Resources of the Biosphere* (Synthesis of Soviet Studies for the IBP), Vol. 3. Human Adaptation (1976).

RETROSPECTIVE REVIEW

The similarity and differences of adaptive mechanisms of man and animals at the same altitudes of different mountain chains have been described time and again. For example, adaptive changes in the blood system are more pronounced in the Caucasian Mountains than in the

Pamirs and even less so in Tien-Shan. Most of the adaptive reactions in the respiratory and circulatory systems are rather similar. However, there are qualitative differences. Thus, $\dot{V}_{O_2}$ and the basal metabolic rate in the highlanders of the Tien-Shan and the Pamirs appear to be within normal limits or slightly lower than in natives of low and moderate altitudes (Mirrakhimov, 1977). It has been found however that the level of basal metabolism of the Caucasian highlanders is higher as compared with the sea level natives (Pogosbekjan and Bedalova, 1975; Sirotinin and Matsynin, 1976).

The reason for the qualitative and quantitative variations in adaptive mechanisms lies in the climatic peculiarities of the mountain regions as well as in their geophysical and geochemical characteristics. For example, the iodine content in the soil, water and air in the Pamirs and, particularly, in Tien-Shan is very small, which in turn leads to a decrease in the action of the thyroid gland, and thereby reducing the basal metabolic rate (Mirrakhimov, 1977).

The low basal metabolism, reduced heart rate and lowered body temperature, as compared with the normal standard values, are characteristic not only of the highlanders but also of most of the lowlanders of the Kirghiz and Kazakh Republics (Filatova, Kanygina and Fantalis, 1972; Mirrakhimov, 1976; 1977). Obviously, the same applies to the weak manifestation of daily cycles of physiological and some biochemical indices. As for the seasonal cycles of a number of bodily functions, these were shown to be more marked as compared with the daily ones, although not in all indices. Some of them appeared to be negligibly small and are not significant statistically (Filatova *et al.*, 1972; Dzhantleuova, 1975; Barbashova, 1972; 1976a).

Decreased basal metabolism and activity level of the organism's functional systems are not regarded as pathological divergence from the usual standard value. The people living in different geographical regions of our big country with essential difference in climatic, geophysical and geochemical conditions have their own regional standard.

It is quite reasonable to presume that the less pronounced adaptive reactions in the natives Kirghiz and Kazakh plains, during their individual adaptation to high altitude, are due to the lower level of the initial standard value of their functional system activity. It has also been found that the greater the amount of physical activity during ascent or on arrival at a place of high altitude, the more pronounced are the changes in the functional systems (Mirrakhimov, 1972; 1976; Sirotinin and Matsynin, 1976).

It has been observed that the cardiovascular activity of the natives of Tien-Shan and the Pamirs only changes noticeably at altitudes above 3000 m. There is a myocardial hypertrophy of the right ventricle which is largely due to alveolar hypertension. At high altitudes (up to 4200 m) myocardial hypertrophy of the left ventricle is also reported.

This seems to be caused by both the increased blood volume and increased blood viscosity. Capillary circulation and permeability were also investigated and their changes described (Mirrakhimov, 1977).

In the natives of the Caucasus the red blood cell count is changed at altitudes of about 2100 m, while residents in the Pamirs and Tien-Shan show changes in their red blood cell count only at altitudes exceeding 3500 m. In addition, changes in erythrocytosis are also observed in the properties of the red cells, these changes include the following: the time of reticulocyte maturation and the erythrocyte life span are shortened, macrocytosis occurs and the haemoglobin content of the individual erythrocytes is slightly augmented. Moreover, there is an increase in the rate of glycolysis as well as in the activity of the monophosphate shunt: also observed is an augmentation of the erythrocyte's osmotic resistance, the 2,3-diphosphoglycerate (2,3-DPG) content, haemoglobin stability to alkaline denaturation (Barbashova, 1970; 1977), and its electrophoretic mobility (Sirotinin *et al.*, 1976). The highlanders and the newly-arrived lowlanders were found to exhibit significant changes in their blood coagulation and fibrinolytic activity (Avarbakieva and Popeleshko, 1975; Issabaeva, 1972; Agadzhanjan, Issabaeva and Elfimov, 1973).

It was also found that the physical work capacity of the natives of Tien-Shan and the Pamirs, living at 2500 m is markedly higher than that of the plain dwellers; while exercise tolerance in highlanders residing at 3600 m and higher was found to be reduced as a result of inadequate regulation of the cardiorespiratory system (Mirrakhimov, 1977). The increase is an observed in the work capacity of the plain dwellers during their gradual ascent under an active life regime in the mountains (Sirotinin *et al.*, 1976). Experimental data obtained on hypoxia-adapted animals showed that an increase in the resistance of the organism is due to the changes of both activity of the functional system and the processes at the cellular level (Barbashova, 1969; 1970).

The state of the central nervous system as well as mental performance was studied in healthy men during adaptation to an altitude of 3200 m (Tien-Shan). It appeared that deterioration of mental performance occurred only during the first few days (Mirrakhimov *et al.*, 1975). Studies of the functional condition of sense organs in mountaineers during the ascent to Lenin Peak (the Pamirs, 7134 m) showed an increase in auditory and pain sensations and a slight improvement of the visual sensitivity. This increased sensitivity is only observed up to 3500 m during the ascent. At altitudes of 5200–6100 m and higher the functional condition of the sense organs was impaired (Gippenreiter, Ivanov and Khachaturjants, 1972).

Anthropological, serological and dermatoglyphic data were collected from children and adolescents living at high altitudes in the Pamirs. They showed markedly slow patterns of development and sexual maturation compared with the data for plain dwellers of Kirghiz (Miklashevskaya and Solovjeva, 1976). Analysis of the morphological features of the native children of Tien-Shan and the Pamirs revealed that at an altitude above 3600 m there was a decrease in the heart rate (as compared with that of lowlanders) even in a newborn infant, and that this characteristic persists throughout their lifes. Cases of right ventricular hypertrophy at 2200 m were reported for 6-month old babies, while at altitudes 3600 m and higher, hypertrophy of the right ventricle occurs in all the newborns (Mirrakhimov, 1977).

The physiological processes of fertility and pregnancy in women living in different mountain regions were studied, as well as the epidemiology of certain internal diseases occuring at different altitudes of the Tien-Shan and the Pamirs (Mirrakhimov, 1977).

REVIEW OF CURRENT INVESTIGATIONS

This review covers the material of the 5th All-Union Conference on environmental physiology, biochemistry and morphology held in Frunze at the end of 1977. The topics discussed at this conference are published in three books: Book I: 'Physiology and Pathology of Adaptation to Environmental Factors'. Book II: 'Ecological and Physiological Studies in Nature and Experiment'; Book III: 'General Problems of Environmental Physiology. Ambient Temperature and Metabolism of an Animal Organism in Nature and Experiment'. The main trends in the research of mountain physiology and medicine will now be discussed.

Effects of meteorological and heliophysical factors

Alterations in solar activity and geomagentic fields bring about changes in respiration and blood circulation as observed in natives and non-permanent dwellers of mid-altitudes (Issyk-Kul, 1800 m) and those of low altitudes (Frunze, 760 m). Individuals newly-arrived in the mountains from the plain or vice versa appeared to be most affected by these changes. These subjects showed a marked increase in heart rate and peripheral vessel resistance, but a decrease in maximal lung ventilation and blood oxygenation (Pokotilo and Kadyrkhanov, 1977).

Cycle Research

Diurnal and seasonal cycles of haemodynamics were studied taking a number of physiological parameters into consideration (Abyldabekov, 1977).

The studies covered the following topics: blood content electrolite content of saliva and urine (Nurdavletova and Turkmenov, 1977) of lowlanders (760 m) and highlanders (3200 m) of Tien-Shan; the haemodynamics, respiration and body temperature in sheep and lambs living on the plain and mountains (3800 m) (Tumakova, 1977). As in previous studies, the data obtained showed that daily cylces in humans and animals of Kirghizia, particularly when living at high altitudes, are not significant. More pronounced are the seasonal changes, particularly in the lowlanders.

Laboratory experiments showed a clear correlation between diurnal cycles of resistance to hypoxia, of variation in the pO_2 and pCO_2 values in the alveolar air, and of electrolite and corticosteroid hormone levels in human and animal blood. Resistance to hypoxia was found to follow a definite seasonal pattern; in rats this parameter is higher in autumn (September–October) and lowest in winter (January–February) (Agadzhanjan, 1977).

Respiration

Further research into the area of the respiratory mechanisms of the highland natives is being carried out. The emphasis is upon 'hypoxic deafness', i.e. decrease in the ventilatory response to hypoxic stimuli characteristic for some dwellers. Changes in haemoreceptor sensitivity to CO_2 were discovered. There is sufficient evidence that hypoxic 'deafness' can hardly be regarded as a positive adaptive reaction. (Mirrakhimov, 1977).

Cardiovascular system

Previously obtained data on regional specific changes in capillarization were confirmed as well as the observations on the increase of capillar permeability in various organs and tissues of animals living in Tien-Shan (1600–3200 m) and humans in the Pamirs (Khamitov and Zakharov, 1977; Shidakov *et al.,* 1977; Kaznatcheev and Egunova, 1977). Changes in the morphlogy of the microcirculatory lymphatic bed in the dog's pericardium were observed during adaptation to an altitude of 3600 m in the Pamirs (Abdurachmanov and Juldashev, 1977).

Blood system

Data have been obtained showing different mechanisms of adaptation to hypoxia in the blood system in wild rodents depending on the length of their sojourn at high altitude. A change in erythrocytosis and an increase in the haemotocrit and haemoglobin content were reported in the Caucasian species of the ground squirrels, living at altitudes about 1400 m for 15 years and at 3000 m for 25 years. On the other hand, the ancient species of ground squirrels that have inhabited the Caucasus at 1800–2200 m for over a million years, showed lower values in erythrocytes, haemoglobin and in haemotocrit than in their lowland counterparts, despite the fact that in the species living at high altitude the bone marrow erythropoiesis was stimulated and the activity of erythropoietins in the blood plasma was increased. The number of circulating erythrocytes and the haemoglobin content in the highland animals were higher than those in lowlanders owing to the increased body blood volume. The low concentration of erythrocytes and haemoglobin in the blood was due to dilution by a greater volume of plasma as compared with the species living in the plains.

It has been proposed that this type of adaptation to hypoxia indicates not only a higher blood oxygenation per unit of body weight, but also it provides an adequate level of rheological properties of blood. The latter properly is extremely important because the blood of the mountain-dwelling ancient ground squirrels is supplied by macrocytes alone which might have caused a rise in blood viscosity, had it not been diluted by plasma. However a theory exists that the current concept of a possible adaptation to hypoxia, without the accompanying erythrocytosis, does not unconditionally hold true and must, therefore, be revised (Barbashova, 1976b; 1977; Tarakanova, 1977).

Significant differences have been found in the haemoglobin electrophoretic pattern of the original mountain- and lowland-ground squirrels, but the 2,3-DPG content remains the same. Ground squirrels living at a high altitude for 25 years, showed no changes in their haemoglobin fractions but the 2,3-DPG content was higher than in the lowland counterparts. These data lead to the proposal that different mechanisms of regulating the oxygen affinity of the haemoglobin depend on the population history (Grigorieva *et al.*, 1976; Grigorieva, 1977).

A rise in the 2,3-DPG content was also detected in the erythrocytes of humans from the third day after transfer from sea level to 3200 m (Tien-Shan). The affinity of haemoglobin for oxygen was in this case reduced, which was shown by the rise of the P_{50} on the oxyhaemoglobin (HbO_2) dissociation curve (Son, 1977).

It could be demonstrated that changes in coagulant properties are largely due to altitude and climate. It is assumed that stimulation of non-enzymatic fibrinolysis and reduction of blood coagulation are related to changes in the functioning of endocrine glands, particularly to the release of adrenalin into the blood (Issabaeva and Ivanova, 1977).

Endocrine system

A study of the endocrine glands of both human and animal organisms was investigated — at rest and during muscular activity — in relation to the length of sojourn in the mountains and depending on the altitude of the locality. It was found in healthy male natives of Tien-Shan (3200 m) that the adrenalin and noradrenalin levels in urine was increased, while the levels of the 17-ketosteroids and aldosterone were decreased compared with the natives of the plains (Isagalieva, 1977).

As in previous studies a moderate hypothyroidism was found in mountain dwellers, sheep, cows and yaks living at different altitudes of Tien-Shan and the Pamirs. The length of the animals' stay at altitude seems to be of great importance. Thus examination of the ground squirrels populating the Caucasian mountains during 25 or 15 years showed that their thyroid functional activity and morphology was drastically inhibited. While in ancient ground squirrels, which inhabited the mountain area during millions of years, the thyroid functional activity was only slightly lower than in their sea level counterparts (Tavrovskaya, 1977). The same animals also showed a significant difference in the structure of the supraoptical nucleus in peptidergic neurosecretory formations of the hypothalamus (Krasnovskaya, 1977).

Immunity system

Systematic research into immune reactions in high-altitude natives and those living at sea level during adaptation to hypoxia was started a relatively short time ago. Observation of healthy adult men during the first stages of adaptation to the Pamirs revealed inhibition of the complement and lysozyme activity, reduction in the ability of the T and V lymphocyte to transform into blasts as well as inhibition of the immunoglobins, A, M, and G synthesis. The authors regard this as a stress response. The functional activity of the immunogenic apparatus became normalized towards the 30th day of the sojourn in the mountains (Mirrakhimov *et al.*, 1977). Phase alterations of the leucocyte phagocytic function, of serum lysozyme activity, as well as that of B cells and humoral factors of nonspecific immunity have been reported for rats during their adaptation to 3200 m in Tien-Shan (Aldzhambaev *et al.*, 1977; Kitaev *et al.*, 1977).

Energy metabolism

Studies of the cell energy metabolism in animal organisms during adaptation to hypoxia have not added much to our current knowledge of the problem. This seems to be a most challenging aspect, obviously necessitating totally new approaches. It is well known now that at those altitudes which enable adaptation and normal functioning of the organism, disturbances in tissue respiration occur only in the initial stages, after which respiration comes back to normal. This is presumably due to increased capillarization of tissues, higher speed of blood flow, increase in the cell myoglobin content and, according to current concepts, low 'critical' level of pO_2 in the mitochondria (Antonov, 1977; Vymjatina, 1977; Plekhina, 1977). It has been suggested that a possible change in the regulation of tissue respiration occur, due to an increase in the amount of endogenous metabolites, such as ATP and phosphocreatinine (Khavkina, 1975). This may very well be the case as a result of moderate short-term hypoxia. However, studies carried out on the natives of high altitudes invariably demonstrate differences in the metabolic state of tissues, as compared with that of sea level dwellers.

Thus, activity of cytochrome-oxidase in the myocardium of the wild mountain forestry mouse, populating Caucasian altitudes (1800–2200 m), appeared to be higher than in the sea-level species (Sharafutdinova and Khavkina, 1977). Increased amounts of carotenoids in the tissues have been reported for some Caucasian rodents native to high altitude (Karnaukhov and Fedorov, 1977). The myocardium of the Altai and Pamirs mountain yaks, living at 3000–3600 m, have been found to possess mitochondria of a specific structure, i.e. they are formed with an increased surface area of cristae. The same animals showed elevated values for the amount of glycogen storage granules lying between myocardial cells. Presumably, the newly observed features provide for a high level potential energy production of the myocardium, thus preventing development of hypoxia (Zhapharov and Mirrakhimov, 1976).

This paper describes only the main topics of research which are being studied in the USSR at present. Due to lack of space we did not review the many other research projects in the USSR.

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Review of Recent Studies on Biological Effects of High Altitude in India

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INTRODUCTION

The interest in high altitude studies in India has recently increased for a variety of reasons. These reasons include the defence of our country, exploration of mineral wealth, and instinct for adventure, recreation and the natural beauty of mountains. It follows therefore that a large number of people will live at high altitudes or visit high altitudes. Solar radiation, hypoxia, hypobaric pressure and cold are the primary factors which adversely affect the physiological processes in man at high altitude. The three main illnesses which can afflict new arrivals to high altitudes and their inhabitants at high altitude are *acute mountain sickness* (AMS), *high altitude pulmonary oedema* (HAPO), and *high altitude pulmonary hypertension* (HAPH). Our experience of these illnesses was gained on our Northern borders and dates from 1962. A large amount of relevant information has been collected since then on the clinical and pathophysiological aspects of the various disorders. This communication presents a review of the progress up to date on these subjects.

ACUTE MOUNTAIN SICKNESS AND HIGH ALTITUDE PULMONARY OEDEMA

Symptoms and cause

Rapid ascent, exercise and oliguria are the common precipitating factors of AMS and HAPO. Singh *et al.* (1969b) regard AMS and HAPO as clinical variants of the same disorder. In both there is a definite time lag between arrival at high altitude and onset of the illnesses. Either or both of the illnesses may occur in a patient.

In contrast to symptoms of hyperventilation and tachycardia which occur on immediate arrival at high altitude and respond to oxygen inhalation, the symptom-complex of AMS is not readily relieved by oxygen therapy and necessitates diuretic therapy in addition.

A study on AMS in 1925 men, 18–53 years old, in the Himalayas between 11 000 and 18 000 ft revealed that there was no direct correlation between altitude and the severity of the illness. Mild, moderate and severe cases occurred at all altitudes (Singh *et al.,* 1969b). A time lag of 6–96 h between arrival and onset of symptoms rules out any direct relation between hypoxia and AMS. During this period there is clinical evidence of respiratory dysfunction indicated by slow, irregular or *Cheyne-Stokes* breathing, pulmonary congestion and antidiuresis. Clinical features of AMS have been ascribed to hypoxia, pulmonary congestion, increased cerebral blood flow, increased cerebrospinal-fluid pressure and cerebral oedema. Symptoms in untreated cases, in order of frequency, are headache, nausea, anorexia, dyspnoea, muscular weakness, fullness or pain in chest, giddiness, vomiting, disinclination to work, thirst, indigestion, flatulence, constipation, tachycardia, palpitation, hysterical outbursts or other disorders of behaviour, lack of concentration, mental impairment or confusion, fever, pain in the legs, cough, oedema of the legs and feet, hallucinations, diarrhoea, difficulty in micturition, epistaxis, pain in the abdomen, elevated blood pressure (above 160 systolic, 100 diastolic), low blood pressure (below 110 systolic, 75 diastolic), blackouts, haemoptysis, incoherent speech, lack of response to questions, sudden collapse in bed during sleep, visual disturbances, stupor, seizures, coma and paralysis. In very severe cases with elevated pressure of cerebrospinal fluid (CSF), symptoms of cerebral tumour may be mimicked and, in the neurological form, papilloedema and retinal haemorrhages may be encountered (Singh *et al.,* 1969b; Clarke and Duff, 1976).

The pathogenesis of AMS is largely obscure. However, the general consensus is that there is an initial hypersecretion of adrenal corticosteroids, antidiuretic hormone and aldosterone, causing renal retention of water and electrolytes and a marked intracellular shift of fluid (Singh *et al.,* 1969b; Sutton, 1971; Singh *et al.,* 1974; Currie *et al.,* 1976). The above mechanism operates concomitantly with effects of hypoxia causing peripheral venous constriction with eventual increase in pulmonary blood volume, congestion and frank HAPO. These symptoms in turn lead to oliguria and development of cerebral oedema which causes headaches and other neurological disorders. The elevation of CSF pressure results in papilloedema and retinal haemorrhages.

Recently Maher, Levine and Cymerman (1976) observed coagulation changes suggestive of coagulopathy in a group of subjects who developed AMS on acute exposure to high altitude (simulated altitude

4400 m). Previous studies in patients who developed HAPO with acute exposure at high altitudes revealed presence of platelet and fibrin thrombi in capillaries of lungs and other organs (Arias-Stella and Kruger, 1963; Hultgren, Spickard and Lopez (1962). Our own studies conducted in the Himalayas confirm the basis of coagulopathy in this disorder (Singh *et al.*, 1965a; Singh and Chohan, 1974). The occlusions at the capillary and venular level at several places may lead to over-perfusion and result in patchy oedema formation in lungs (Hultgren, 1967). Such scattered thrombotic occlusions in cerebral microvasculature might be expected to result in cerebral oedema and raised CSF pressure with consequent compression and symptom-complex of AMS.

It will be relevant to mention here that an element of exertion is invariably associated with development of AMS. It is well known that strenuous exercise results in a hypercoagulable state which is evident during and in the post-exercise period. This condition arises due to the following factors: a rise in factor VIII (Rizza, 1961; Collen, 1974; Davis *et al.*, 1976); factor VIII-related antigen (Prentice *et al.*, 1972; Denson, 1973; Collen, 1974); platelet count and platelet retention (Davis *et al.*, 1976); and shortening of the activated partial thromboplastin time (Iatridis and Ferguson, 1963) despite a rise in fibrinolytic activity (Biggs, MacFarlane and Pilling, 1947; Iatridis and Ferguson, 1963; Collen, 1974; Davis *et al.*, 1976). The shortening of the activated partial thromboplastin time has been ascribed to an increase in factor XII level (Iatridis *et al.*, 1963) which has been reported to occur on acute exposure to high altitude in healthy subjects (Singh *et al.*, 1974). It seems that combined ill effects of hypoxia and hyperexercise lead to adverse blood coagulation in susceptible individuals who develop AMS. In these individuals the compensatory fibrinolytic activity fails to rise as in those subjects who suffer from HAPO (Singh *et al.*, 1974; Singh, Chohan and Mathew, 1969a). The details of adverse changes in blood coagulation in subjects of HAPO and HAPH are described later in this paper.

It is interesting to note that Ogston and Fullerton (1961) found, within limits, increased fibrinolytic activity proportional to the amount of exercise undertaken by a subject; however, in untrained subjects, unaccustomed to exercise, fibrinolytic activity was found to remain reduced after prolonged strenuous exercise and an anti-activator release was postulated. This might well be the case with the subjects who become victims of AMS and HAPO. It seems plausible therefore, that a planned study of the fibrinolytic system, blood coagulation factors and platelet functions in AMS is required to ascertain the mechanism(s) of development and to institute the rational therapy in this illness.

Treatment

Acute mountain sickness of mild intensity is a self limiting illness and the early phase of severe symptoms subsides within 2–5 days but complete recovery takes few weeks to months. Those who fail to adapt within 6 months have to be evacuated to the plains (Singh *et al.*, 1969b).

Induced diuresis is the mainstay of treatment. Diuretics, in particular furosemide, have been used effectively to reverse the fluid retention (Singh *et al.*, 1969b; Sutton, 1971). Furosemide is used in a dosage of 80 mg every 12 h for 2 days and with this regimen symptoms and signs of AMS are relieved within 6–48 h. In severe cases of AMS, especially when associated with HAPO, morphine (15 mg) added with first dose of furosemide has been found to bring about more effective diuresis, reduce pulmonary blood volume, alleviate anxiety and induce mild sleep; all of these factors are beneficial in promoting recovery. In more severe cases with neurological involvement betamethasone combined with furosemide has proved to be lifesaving (Singh *et al.*, 1969b).

Furosemide has not found favour with some authors as mentioned recently in *Man at High Altitude* by Heath and Williams (1977). Acetazolamide, a less potent diuretic, has been advocated by some to counteract respiratory alkalosis (Cain and Dunn, 1966; Carson *et al.*, 1969). Aspirin has also been used to relieve headache, a component of AMS (Singh *et al.*, 1969b; Currie *et al.*, 1976). Recently spironolactone, an antialdosterone, has been used as a successful prophylactic against AMS (Currie *et al.*, 1976). The regimen used was spironolactone in a dosage of 25 mg three times a day for two days preceding and during the periods spent at altitudes above 3000 m. Spironolactone is a safe and short-term low dosage diuretic and has the added advantage of promoting retention of potassium ions. Since aldosterone levels are significantly lowered at high altitude (Maher *et al.*, 1975) it remains to be seen as to what extent the lack of aldosterone is responsible in the development of AMS. A large scale trial of spironolactone in the management of AMS is desirable.

In view of the new finding relating blood coagulopathy to AMS (Maher *et al.*, 1976) and HAPO (Singh and Chohan, 1974), the search of appropriate agents like anticoagulants, antiplatelet adhesive drugs and fibrinolytic agents to cure these disorders is required and a controlled trial necessary. At present furosemide is a drug which combines the characteristics of being a stimulant of fibrinolytic system and inhibitor of platelet activity (Chohan, Singh and Vermylen, 1977a; Chohan *et al.*, 1977b). Furosemide has been extensively used world over in the management of AMS and HAPO, and has been found to be effective in reversing the adverse changes in blood coagulation, fibrinolytic activity and platelet functions associated with these illnesses (Singh and Chohan, 1973). The details of furosemide's actions are discussed later.

CHANGES OF BLOOD COAGULATION AT HIGH ALTITUDE

Haemostasis at high altitude

The first few days at high altitude in recent arrivals are critical from the point of view of haemostasis. On arrival at a place of high altitude there is a tendency towards hypercoagulation associated with an increase in platelet count, factors X and XII, and thrombotest activity (TA), reflected by decrease in prothrombin time (PT), bleeding time (BT), clotting time in glass (CT-gl) and silicone (CT-sl), and stypven time (ST). Clot retraction is impaired. This hypercoagulation state is countered by a compensatory rise in fibrinolytic activity reflected by reduction of clot-lysis time (CLT), plasma fibrinogen and factor VIII (Singh and Chohan, 1972a; 1974). This hypercoagulative state persists throughout the fortnight after arrival and then starts regressing. On Day 3, factor V decreases, BT and ST are further reduced, and factor VIII shows a rise. On Day 7, a progressive rise occurs in factor V, VIII, X and XII, TA, platelet counts and platelet factor III (PF-3). CT-gl, CT-sl, PT and ST are further shortened. On Day 14, haematocrit rises and of all the parameters, factors V and X and clot retraction return to normal. Throughout the fortnight, factor XII remains high, CLT is short, thrombin clotting time is prolonged, and platelet adhesiveness remains within normal range (Singh and Chohan, 1972a; 1974). It thus seems that immediately on arrival at high altitude there is a tendency towards a hypercoagulation state associated with a compensatory increased fibrinolysis (Singh and Chohan, 1972a; 1972b; 1974; Chohan, Singh and Balakrishnan, 1974).

An adaptative change made during continuous stay at high altitude, is further regression of the hypercoagulation state indicated by persistent short CLT, prolonged BT, CT-sl, PT, ST and reduced thrombotest activity. Platelet adhesiveness, PF-3, factors V, VIII and XII and clot retraction are restored to normal. The reduction in hypercoagulation during prolonged stay at high altitude is partly checked by significant increase in plasma fibrinogen (Singh *et al.*, 1972a; 1972b).

High altitude pulmonary oedema

In HAPO evidence has been previously brought forward (Nayak, Roy and Narayanan, 1964; Singh *et al.*, 1965a) of widespread sludging of red blood cells (RBC) and formation of thrombi within the alveolar capillaries, venules and some branches of the pulmonary arteries in the lungs, the glomerular and the peritubular arteries in the kidneys, the sinusoids of the liver, and the intestinal blood vessels. There is a time lag from 6–96 h between arrival at high altitude and onset of HAPO. The majority of cases occur within the first 4 days and the chances of developing pulmonary oedema become remote after 7–14 days (Singh *et al.*, 1965a). This incidence seems to run parallel with the state of hypercoagulability developing at high altitude (3700 m) as reported above.

Blood coagulation studies carried out in patients suffering from HAPO at 3700 m compared with suitable controls revealed a causal connection between changes in fibrinolytic activity, blood coagulation factors, platelet functions, and formation of thrombi in the pulmonary vasculature. The following changes have been observed at the very onset of the illness: fibrinolytic activity is reduced; plasma fibrinogen and factor VIII are increased; factor XII is decreased; platelet adhesiveness and PF-3 are increased and are associated with numerical fall in platelet count; electrophoretic mobility of platelets is reduced; clot retraction is markedly impaired; the haemotocrit, factor V, and factor X are moderately increased and thrombin clotting times is moderately decreased; the integrity of platelet plasma membrane and release reaction remain intact; both arterial and venous ADP levels are low and there is evidence of sequestration of ADP in the pulmonary bed. On examination of peripheral blood smears of HAPO patients, by light microscopy, larger and more young platelets are found in aggregates. Furthermore, electronmicroscopic studies of platelets in patients reveal normal degranulation, numerous pseudopodia and sound plasma membrane showing, thereby, that platelets of HAPO patients are active both structurally and functionally. From the above account it would appear that in HAPO patients PF-3 and the substrates for thrombin and fibrin generation are provided abundantly. Platelet factor III provides an active catalytic surface for the interaction of plasma coagulation factors which lead to thrombin generation, followed by consolidation of the platelet plug, degranulation of platelets, further release of PF-3 and ADP, and fibrin formation. Thus the coagulation process in HAPO seems to result in formation of platelet and fibrin thrombi in the lungs at the capillary and venular level, which impede the pulmonary blood flow and aggravate the disease (Singh *et al.*, 1972a; 1974). In the event of breakdown of the fibrinolytic system i.e. in patients suffering from HAPO (Singh, *et al.*, 1969a; Singh *et al.*, 1972a; 1974), it is conceivable that the pendulum will swing to hypercoagulation which could prove fatal unless speedily treated with an appropriate drug (Singh *et al.*, 1973) effecting clearance of pulmonary congestion and removal of impediment to blood flow in the microcirculation in lungs and other affected organs.

Concentrations of immunoglobulins IgG, IgA and IgM are markedly raised in HAPO patients as compared to controls (Chohan, 1971; Chohan, Balakrishnan and Talwar, 1971; Singh *et al.*, 1972a; 1974; Chohan *et al.*, 1975b). It is possible that IgG and IgM are adsorbed onto the surface of platelets, altering their mobility, increasing their aggregation, and enhancing the release of ADP from them. A further release of ADP promotes PF-3 activity which amplifies the coagulation process. This enhanced synthesis of immunoglobulins possibly makes the previous HAPO sufferers, who are already geared up to produce more immunoglobulins, more susceptible to develop HAPO than unexposed subjects (Chohan *et al.*, 1975b). This increase in immunoglobulins at high altitude occurs as a result of higher B-lymphocyte population (Chohan, *et al.*, 1978; Singh and Chohan, 1978).

We have recently observed a dichotomy of immune responses in HAPO. On the one hand immunoglobulins are increased, and on the other, cell mediated immunity (CMI) is markedly impaired (Singh *et al.*, 1978) which is evident by reduction in number of T-lymphocytes, lymphocyte migration index, PHA-blast transformation of lymphocytes, and absent DNCB-response in the acute stage of illness. The derangement of CMI helps to promote persistance of immune complexes, activated clotting factors and end products of blood coagulation and thereby accentuates intravascular coagulation. Inhibition of fibrinolytic activity is known to block the reticuloendothelium system (Lee, 1962) which leads to ineffective immune clearance in the generalized Schwartzman reaction attendant with its consequent fibrin deposition in several organs. In view of diminished fibrinolytic activity and impaired CMI it is probable that an element of immunological deviation exists in HAPO and this deviation needs consideration in the pathogenesis of this disorder.

High altitude pulmonary hypertension

Marked pulmonary hypertension is present during the acute phase in all cases of pulmonary oedema at high altitude (Singh *et al.*, 1965a); it may even precede its development (Reeves and Grover, 1975). This condition seems to be induced by raised capillary pressure as a result of widespread occlusion of capillaries with thrombi in the lungs (Singh *et al.*, 1965a).

Although pulmonary hypertension in permanent residents of a high altitude area is well known, its occurrence in temporary residents has been documented only by Singh *et al.* (1965b). Age is no bar for its development. In our subjects, who are temporarily posted from sea level to altitudes between 3690 and 5540 m for 2–3 years in the Himalayas, the symptoms of pulmonary hypertension begin after a stay of 5–42 months. After the initial onset of the disease, periodic returns to sea level for 2–3 months at a time, once a year, do not alter the picture. The hypertension either persists at sea level or, if it abates, it reappears within 2–3 weeks after the individual returns to high altitude. Pulmonary vasoconstriction, increased pulmonary blood volume, and polycythaemia may have some role in the pathogenesis of high altitude pulmonary hypertension (HAPH), however they do not explain its slow disappearance or persistence when the subjects return to sea level. In Andean inhabitants, between altitudes of 14 000 and 16 000 ft, it accrues from persistence of foetal pattern of pulmonary vasculature resulting in muscularization of pulmonary arteries and arterioles. In our subjects exposed to the Himalayan altitudes pulmonary hypertension is based on abnormalities of blood coagulation induced at these high altitudes.

In HAPH patients, in comparison with corresponding normal (control) residents, after 2 years stay at high altitude, platelet adhesiveness, PF-3, factor V, and factor VIII are significantly increased; plasma fibrinogen levels are significantly decreased; and the activity of factor X, factor XII and thrombotest are moderately increased. The main difference in the hypercoagulative state in HAPH patients and the controls in an increase in platelet adhesiveness, PF-3, factor V and factor VIII (Singh *et al.*, 1972a; 1972b). The controls who do not develop HAPH show only increase in fibrinolytic activity which is normally enhanced at high altitude (Singh *et al.*, 1972a; 1972b; 1974; Chohan *et al.*, 1974). Though the fibrinolytic activity of the blood is increased at high altitude, there are certain factors lacking in HAPH patients. This requirement seems to be related to the Hageman-dependent pathway of fibrinolysis since the level of factor XII returns to normal with restoration of fibrinolytic activity on return to sea-level (Singh *et al.*, 1972b).

Electronmicroscopic studies of platelets in HAPH subjects do not reveal any gross abnormality. Electrophoretic mobility of platelets of HAPH patients is reduced and the reduction is related to raised plasma fibrinogen, clotting factors V, VIII, and possibly some other factor in HAPH plasma (Singh *et al.*, 1972a; 1972b; Chohan *et al.*, 1971). This is concluded from the fact that when normal platelets are suspended in HAPH-plasma their mobility is reduced.

In both HAPO and HAPH, as against their respective controls, the abnormal state of blood coagulation is associated with increased platelet adhesiveness, platelet factor III, factors V, VIII and X, and the haematocrit values. The outstanding difference between HAPO and HAPH is in the fibrinolytic activity which is reduced in the former but remains relatively increased in the latter (Singh *et al.*, 1972a).

The adverse changes in blood coagulation, fibrinolytic activity and platelet functions in above disorders, especially in HAPO, have been reversed with the use of furosemide (Singh *et al.*, 1973). The fashion in which these changes can be affected by this drug is discussed below.

REVERSAL OF ADVERSE CHANGES IN BLOOD COAGULATION BY FUROSEMIDE

Furosemide* alone or in combination with morphine and betamethasone is the mainstay of treatment of HAPO (Singh, 1967; Singh *et al.*, 1967; Singh, 1971). The beneficial effects of furosemide administration in HAPO become manifest within 30 min and lead to an uneventful recovery (Singh *et al.*, 1973). Apart from inducing rapid diuresis and reducing pulmonary blood volume, furosemide enhances fibrinolytic activity (Singh *et al.*, 1973; Chohan *et al.*, 1977b; Bruhn *et al.*, 1975); decreases concentrations of factors V, VIII, X, and thrombotest activity; increases factor XII; reduces platelet factor III and platelet adhesiveness, and improves clot retraction. Thus by virtue of rapid induction of diuresis and by its ability of reversing adverse changes in fibrinolytic activity, blood coagulation, and platelet function, furosemide removes impediment to and improves pulmonary blood flow at the capillary and venular levels in HAPO patients.

Furosemide also exerts an inhibitory effect on primary aggregation induced by adenosine 5'-diphosphate, both *in vitro* and *ex vivo*. An inhibitory effect of furosemide on platelet secretion has been demonstrated by studying its effect on the release of platelet factor and of ^{14}C-serotonin. This drug also prolongs the latent period before thrombofax – collagen-induced platelet aggregation – again both *in vitro* and *ex vivo*. During *in vitro* experiments, the concentration of furosemide ranges between 0.5 and 2.5 mM for its inhibitory effects. For *ex vivo* experiments 40 mg of furosemide by injection has been found effective (Chohan *et al.*, 1977a).

Since furosemide increases the electrophoretic mobility of platelets in normal subjects (unpublished data), the restoration of the Hageman factor following furosemide adminstration (Singh *et al.*, 1973) may be responsble for this effect. Hageman factor, which is a sialoglycoprotein, is easily adsorbed on the platelet surface and increases its negative electric charge.

The above effects of furosemide seem to depend on its vasodilatory activity, cyclic-AMP phosphodiestrase inhibitory and adenylcyclase stimulatory capacity, and its influence on the Hageman factor-dependent fibrinolytic system. Depending on the following

*Furosemide is a quickly acting diuretic, preventing the reabsorption of water in the kidney, in particular in the Loop of Henle (the U-shaped loop of the uriniferous tubule of the kidney) and therefore accelerating diuresis. It is applied in serious lung or brain oedema.

conditions the integrity of the renal parenchyma is intact and diuresis is effective (Singh *et al.*, 1973; Bruhn *et al.*, 1975; Chohan *et al.*, 1977b). Cyclic-AMP inhibits synthesis of prostaglandin endoperoxide (PGG_2), which is the immediate precursor of thromboxane A_2, this in turn affects secretion and aggregation of human platelets (Malmsten, Gramstrom and Samuelsson, 1976). Platelet aggregation induced by prostaglandin G_2 (PGG_2) has been shown to be inhibited by furosemide (Malmsten *et al.*, 1975). Furosemide also inhibits the release of ^{14}C-serotonin from platelets (Ingerman, Smith and Silver, 1976), and the formation of malondialdehyde, an indicator of platelet prostaglandin synthesis (Ingerman, *et al.*, 1976).

In an attempt to elucidate the mechanism of fibrinolytic action of furosemide simultaneous determination of plasma fibrinolytic activity, measured by the fibrin-plate method, and urokinase excretion in urine, has been carried out after an intravenous injection of 40 mg furosemide. While plasma fibrinolytic activity increases within 30 min of the injection and attains a peak after 6 h, urokinase excretion disappears initially and returns to normal after 3–6 h (Chohan *et al.*, 1977b). The reduction of urokinase after furosemide is an apparent effect of diuretic-induced dilution whereas increased plasma fibrinolytic activity seems to be the result of spill over of a plasminogen activator or urokinase from renal parenchyma, however, it is debatable whether the plasma plasminogen activator is the same as urokinase in this situation. Some workers suggest that activation of fibrinolytic mechanism by furosemide and another diuretic, bumetanide, may be due to their direct action or due to increased sympatho-adrenal activity induced by the brisk diuresis (Mackie *et al.*, 1976). The effects of certain metabolites of furosemide cannot be ruled out since the peak response is attained after 6 h of administration of the drug (Chohan *et al.*, 1977b). In support of this concept is the fact that platelet aggregation is found to be more disturbed at 6 h rather than 10 min after injection (Chohan *et al.*, 1977a). Furosemide is strongly bound to plasma proteins (Mudge, 1971) and it may be slowly released from its stores in liver and kidneys (Seno *et al.*, 1969) to maintain its continuous effects on platelets and fibrinolytic system. The protective effects of furosemide in preventing development of acute renal tubular necrosis and acute renal failure by nephrotoxic drugs in animals (Bailey *et al.*, 1973) and eclamptic crisis in toxaemia of pregnancy (Ngobou *et al.*, 1971) can be attributed to beneficial properties of furosemide. The improvement of blood flow in transplanted kidneys by using a furosemide perfusate (Fernando *et al.*, 1973) has been achieved by its influence on platelet thrombi and fibrinolytic activity which are involved in rejection crisis. Furosemide, therefore, seems to have a rightful place in treatment of diseases where intravascular coagulation is involved and threatens life.

I. SINGH AND I.S. CHOHAN

FROSTBITE AT HIGH ALTITUDE

Occurrence of frostbite continues to be a major problem at high altitude. In frostbite cell damage may result from direct effect of cold or indirectly consequent as a result of hypoxia. Formation of ice crystals in extracellular fluid which occurs, results in hyperosmolarity, with consequent intracellular dehydration and cell death (Carter and Bevin, 1970).

The first effect upon the circulation is vasoconstriction which results from the direct effect of cold upon blood vessels, a sympathetic reflex response, and the effect of cooled blood from other parts of the body upon the hypothalamus (Schumacker and Lempke, 1951). This is followed by capillary dilatation and failure of oxyhaemoglobin dissociation at this low temperature. When thawing occurs there is increased capillary permeability, increased blood viscosity, stasis of red cells, ischaemia, and thrombosis.

To ascertain changes in blood coagulation which lead to thrombotic phenomena in frostbite subjects a study of 15 males, 19–45 years old, stationed between altitudes 3690 and 5540 m in the Western Himalayas, was undertaken within 24 h of developing frostbite and then 4 weeks and 1 year after the incident. For this purpose the fibrinolytic activity, platelet function, antithrombin III and protease inhibitors, and evidences of intravascular coagulation were investigated. To study immunological implications, immunoglobulins, cryoglobulins and plasma proteins were also determined (Chohan *et al.*, 1975a).

In frostbite the course of events causing and following intravascular coagulation were: the presence of increased amounts of fibrinogen degradation products (FDPs) and factor VIII-related antigen in serum; reduced plasma fibrinogen; a fall in platelet counts and haemotocrit; increased platelet adhesiveness; prolonged euglobulinolysis time; marked lowering of antithrombin III and protease inhibitors, alpha-1 antitrypsin and alpha-2 macroglobulin; increased IgG and IgA immunoglobulins and respective cryoglobulins; decreased IgM immunoglobulin and cryoglobulin presumably containing antiplatelet antibodies due to increased consumption; and decreased serum albumin. During the following four weeks of development, the process of thrombus formation continues as is evident from further prolonged euglobulinolysis time, further depletion of plasma fibrinogen, presence of large amounts of FDPs and factor VIII-related antigen, and further decrease in haemotocrit. Antithrombin III and protease inhibitors are further lowered and immunoglobulins are also decreased. At the end of one year, when the recovery is almost complete, euglobulinolysis, platelet adhesiveness, haematocrit, immunoglobulins IgG and IgA, total serum proteins and albumin are restored to normal. Of all the parameters, plasma fibrinogen and platelet counts show a rebound increase and globulins a decrease. Immunoglobulin IgM is slow to recover (Chohan *et al.*, 1975a).

Intravascular thrombosis in frostbite is mainly facilitated by increased platelet adhesiveness and diminished fibrinolytic activity.

The following factors promote increased platelet adhesiveness: injury to endothelium, increased amounts of factor VIII-related antigen, FDPs complexes with fibrinogen/fibrin monomers, increased availability of ADP, a greater number of young adhesive platelets, increased quantity of immunoglobulins including antiplatelet antibodies, and antigen-antibody complexes in the form of cryoglobulins.

Hypergammaglobulinaemia occurs at the cost of albumin-synthesis. The albumin coat protection to platelets becomes inadequate, and platelet aggregation and release reaction are promoted.

Diminished fibrinolytic activity results from release of tissue inhibitors as a result of tissue injury from cold and from increased consumption of protease inhibitors.

Hypercoagulation is also facilitated by raised haematocrit, increased fibrinogen and coagulation factors which are activated by cold conditions and hypoxia at high altitude.

Anticoagulation drugs combined with the property of antiplatelet adhesion, e.g. furosemide administered alone or combined with other compounds, if given in appropriate doses, may be successful in preventing major damage during frostbite resulting from intravascular coagulation. In an attempt to evaluate the efficacy of some drugs in prevention of cold injury, a study was conducted in monkeys and men (Malhotra *et al.*, 1977). During the study thyroid hormones (T_3 and T_4) and tolazoline hydrochloride (Priscol) were administered to observe the effects of raising the blood flow and skin temperature in extremities, on exposure to cold. While thyroid hormones had no such effect, tolazoline hydrochloride was found to raise the extremity blood flow and maintain this area in a relatively warmer state. Tolazoline hydrochloride, 50 mg, administered 2 h prior to the cold exposure without affecting heart rate, oral temperature or oxygen consumption. Combination of these drugs was of no additional value. The clinical trial is yet to be carried out.

IMMUNITY AT HIGH ALTITUDE

Humoral immune responses

There is a qualitative as well as quantitative change in immunoglobulin synthesis in human beings on exposure to high altitudes (3692–5538 m). Increased levels of IgG and IgA have been found in both natives of high altitudes and in those sea level sojourners, who for two years have lived at high altitudes, compared with the lower levels found in sea level residents. During initial acclimatization to high altitude there is marked elevation of IgG and IgA and slight rise in IgM, in the absence of any antigenic challenge. On adaptation, levels of these immunoglobulins decline to a large extent but still remain higher than those of sea level residents. Recent arrivals who suffer from HAPO show pronounced increase in IgG, IgA and IgM immunoglobulins (Singh *et al.*, 1972a; 1974; Chohan *et al.*, 1975b).

Both primary and secondary humoral immune responses after TAB inoculation are of a higher magnitude and of a longer duration at high altitude; this trend is reflected by higher concentrations of immunoglobulins and serum proteins (Chohan *et al.*, 1975b).

On arrival at high altitude, when the stress is greatest, the immunoglobulin synthesis is also at its peak. It is augmented further if there is an antigenic challenge or a concomitant stimulus as happens in HAPO or frostbite (Singh *et al.*, 1974; Chohan *et al.*, 1975a; Chohan *et al.*, 1975b; Chohan *et al.*, 1978). Our results, as well as those of Tengerdy and Kramer (1968), indicate that high altitude itself exerts an immunogenic stimulus. When this high altitude effect is combined with an antigenic challenge, a synergistic effect is obtained. In support of this is the higher incidence of Australia antigen and associated higher immunoglobulins in high altitude natives (Chohan and Balakrishnan, 1973; Chohan *et al.*, 1975b; Dutta and Saha, 1976).

Cell mediated immunity

Cell mediated immunity (CMI) has been recently assessed by determining total and differential leucocyte and absolute lymphocyte counts, T- and B-rosettes, phytohaemagglutinin (PHA)-blast transformation of lymphocytes, lymphocyte migration index (LMI), and DNCB response after application of 1-chloro-2,4-dinitrobenzene (DNCB) on skin in temporary residents and natives at high altitude (3692 m) and compared with sea level residents (Chohan *et al.*, 1978). These parameters have also been studied in patients of HAPO, infectious hepatitis, hepatic amoebiasis, and malaria at high altitude (Chohan *et al.*, 1978; Singh *et al.*, 1978).

An accentuated CMI develops, indicated by increase in PHA-blasts, increased LMI, and intense DNCB response, despite a mild decrease in total leucocytes in the temporary residents and in lymphocytes in the natives at high altitude. While T-rosettes do not show any change in number, B-rosettes are increased in the temporary residents and the natives at high altitude. A qualitative change, therefore, occurs in lymphocytes at high altitude. CMI is equally augmented in the temporary residents as in the natives at high altitude and prevails at a higher plane than at sea level. This property has therapeutic potential.

In HAPO, infectious hepatitis, hepatic amoebiasis, malaria, and natives at high altitude CMI is depressed. LMI is not reduced in infectious hepatitis. In all patients B-rosettes are comparatively high. The implications of depressed CMI in HAPO have been discussed earlier. Depressed CMI in patients contributes to acute flare-up of infectious hepatitis, hepatic amoebiasis, and malaria (imported from plains). On recovery CMI is, however, restored within two weeks by continued stay at high altitude. An increased B cell population accounts for higher levels of IgG, IgA, and IgM immunoglobulins in HAPO and Australia antigen carriers at high altitude.

Continued stay at high altitude results in a significantly lower incidence of infections of bacterial, viral and protozoal origin, diabetes mellitus, hypertension and ischaemic heart disease, asthma and rheumatoid arthritis, gastric disorders, skin diseases, psychiatric ailments and anaemia at high altitude (Singh *et al.,* 1977). These benefits seem to accrue from improved hormonal state, enhanced fibrinolytic activity, accelerated humoral and cellular immune responses, favourable haemodynamics, better cardiac and cerebral functions, improved metabolic functions, and a stable climate at high altitude. Increased fibrinolytic activity and accelerated immune responses at high altitude may act synergistically and provide an effective immune clearance of the antigenic bodies. Rarity of immune-deficient diseases and malignancy at high altitude is probably due to improved immune-surveillance (Chohan, *et al.,* 1978; Singh *et al.,* 1977). It seems that aberrant cells under hypoxic conditions are eliminated effectively and have no chance of survival. Relief of asthma and rheumatoid arthritis may be explained by immune-potentiation at high altitude. A defect in CMI in asthma has been suggested based on reduction of T lymphocytes and diminished response to DNCB and to tuberculin (Al-Tawil, Jazrawi and Taha, 1978).

Impairment of CMI in HAPO coincides with diminsihed fibrinolytic activity (Singh *et al.,* 1978). When fibrinolytic activity improves, the CMI is also restored. In HAPO furosemide speeds up fibrinolytic activity (Singh *et al.,* 1973). Lymphocyte migration is increased when these cells are suspended in a medium containing furosemide (unpublished data). It is likely that furosemide stabilises these cells at the molecular level and enhances their potency. It remains to be seen to what extent furosemide can be used in conditions in which immune-potential is lacking and requires stimulation.

HORMONAL RESPONSES IN RECENT ARRIVALS AT HIGH ALTITUDE

Adrenocortical response

Plasma cortisol levels rise on exposure to high altitude. The rise occurs on the first day at high altitude (3500 m) in control subjects as well as in subjects susceptible to develop HAPO. The levels decline gradually in the control subjects (Singh *et al.*, 1974). In HAPO patients there is a sharp fall in the plasma cortisol level combined with antidiuresis. A rise in the level of antidiuretic hormone (ADH) and oliguria coincide with fall in concentration of plasma cortisol. Before a definitive radiological picture of HAPO develops, a premonition can be obtained from plasma cortisol levels and HAPO/AMS can be averted by appropriate furosemide therapy. This study suggests that when plasma cortisol levels are low, antidiuresis sets in, urinary catecholamines fail to rise, and HAPO is precipitated in susceptible subjects as a result of failure of the normal adrenocortical response under high altitude stress (Singh *et al.*, 1974).

Hypothalamo - pituitary - thyroid response

Our studies reveal that exposure to high altitude leads to enhanced thyroid activity (Srivastava *et al.*, 1976; Singh *et al.*, 1977). In recent arrivals at high altitude the mean thyroid stimulating hormone (TSH) levels are not significantly altered when they return to sea level within 10 days. Neither TSH levels in local residents, nor those in temporary residents at high altitude show a significant difference. The TSH response to TRH is also not significantly altered at high altitude. However, a significant rise in mean total serum T_4 and T_3 concentration occurs soon after arrival at high altitude and persists for 2 weeks (Srivastava *et al.*, 1976; Rastogi *et al.*, 1977; Singh *et al.*, 1977). In the third week T_4 levels tend to normalize whereas wide fluctuations are still evident in serum T_3 levels. The T_3 levels eventually stabilize, and the local and levels tend to normalise whereas wide fluctuations are still evident in serum T_3 levels. The T_3 levels eventually stabilise, and the local and temporary residents at high altitude have higher T_4 and T_3 levels than sea level residents. Both serum T_4 and T_3 levels revert to normal within a week after return to sea level. Continued stay at high altitude is, therefore, associated with higher levels of circulating T_4 and T_3. However, this thyroidal adaptation occurs without significant alteration in TSH levels or pituitary responsiveness to TRH. The enlargement of the thyroid gland seems to be compensatory. Unless nodular changes are present, the size returns to normal on return to sea level.

Rastogi *et al.* (1977) report that with concomitant rise in serum T_4 and T_3 levels, urinary excretion of both T_3 and T_4 is decreased on exposure to high altitude. They suggest these changes could result from complex physiological adjustments on acute exposure to high altitude, e.g. shrinkage of the T_3 and T_4 distribution pools, altered binding capacities of thyroid hormones binding proteins, and reduction in clearance of thyroid hormones from the plasma compartment, and do not necessarily suggest enhanced thyroid activity.

Recently elevated levels of T_4 in arterial blood have been reported in every case of respiratory failure at 2240 m altitude (Bojalil *et al.*, 1978). Whether it is the result of hypoxaemia or respiratory distress, can not be said. The exact role of thyroid physiology in man during acute adaptation to high altitude is still not clear.

CONCLUSIONS

On immediate arrival at high altitude there is a tendency towards a hypercoagulable state which is countered by a compensatory rise in fibrinolytic activity. However, with a continuous stay this state regresses and enhanced fibrinolytic activity persists throughout the sojourn in temporary residents at high altitude.

Occlusive changes in high altitude pulmonary oedema and high altitude pulmonary hypertension are based upon the adverse changes in blood coagulation factors, plasma fibrinolytic activity, and platelet functions. Possibly blood coagulopathy is involved in pathogenesis of acute mountain sickness also and needs further elucidation.

Judicious use of furosemide, in our experience, is still the mainstay of treatment of high altitude pulmonary oedema and acute mountain sickness. The beneficial effects of furosemide are partly due to induction of rapid diuresis and immediate reversal of the adverse changes in blood coagulation, fibrinolytic activity, and platelet functions.

In frostbite evidence of intravascular coagulation suggests that an early institution of anticoagulant and antiplatelet adhesive drugs may prevent damage.

Both humoral and cellular immune responses are accentuated and the immune-surveillance prevails at higher altitudes.

Prolonged stay at high altitude results in a significantly lower incidence of: infections of bacterial, viral and protozoal origin; degenerative diseases including diabetes mellitus, hypertension and ischaemic heart disease; immunological diseases including asthma and rheumatoid arthritis; and gastric, skin and psychiatric diseases. These benefits seem to accrue from improved hormonal state, enhanced fibrinolytic activity, accelerated immune responses, favourable haemodynamics, better cardiac and cerebral functions, improved metabolic functions, and a stable climate.

Augmented fibrinolytic activity, immune responses, and hormonal functions at high altitude could be used to improve health and to accelerate convalescence.

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Human Diseases

Studies on the Effects of Weather and Climate on Respiratory Diseases in the People's Republic of China

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INTRODUCTION

In view of the fact that respiratory diseases in China are most frequent in winter, on theoretical grounds it is logical to assume that an interrelationship should exist between meteorological conditions and respiratory diseases. For the purpose of prevention, since 1971, Hsia and his colleagues have been engaged in an investigation of the effects of weather and climate on respiratory diseases in the People's Republic of China. In this paper, chronic bronchitis, upper respiratory infections and bronchial asthma will be briefly discussed. Full reports have been published during the period 1973–1978 in Chinese periodicals.

CHRONIC BRONCHITIS

Chronic bronchitis is a common disease in China among old age people which recurs every winter; it may eventually cause pulmonary heart disease.

According to a survey of 31 393 people in Shanghai and Kwangtung, Szechwan Heilungkiang, Hopeh and Kansu Provinces, the incidence of chronic bronthitis is 0.8–17.7 %, the annual mean temperature is 1.1–21.1 °C in these places. There is a highly significant negative correlation between the incidence of chronic bronchitis and the mean annual temperature ($R = 0.561, p < 0.01$).

In certain places it was found that patients with chronic bronchitis are suffering most when the mean monthly temperature fell below a certain critical temperature e.g. in Heilungkiang province the critical temperature was −15 °C, in Kansu it was 0 °C.

In order to analyse the deeper causes of the relationship between weather and respiratory diseases during cold weather, several experiments were carried out:

1. The *Chinese Ink Method* was used to determine the speed of secretion in the trachea of mice. It was found that a significant difference exists between controls and the cold stimulated animals, specially at the time when the animals were staying about 5 weeks in a cold environment. During a period of 10–15 weeks it does not appear to be significant anymore.
2. During cold stimulation it was observed that the ciliary activity in the trachea of the rabbit was reduced.
3. If mice inhale aerosols of staphilococcus in a cold environement, the bacterial excretion rate is slower than if the animals are kept in a warm environment.
4. It was found that in mice in a cold environment, after 35 days, some pathological changes in the trachea took place such as hyperplasia of the epithelium and infiltration of white blood cells.

UPPER RESPIRATORY INFECTIONS

Between January 1975–February 1976, Hsia and colleagues studied in Shanghai the influence of meteorological factors on upper respiratory infections. Daily observations were made in a constant population in a machine factory. Certain types of upper respiratory infections were observed for a etiological study. The following virus incidence frequences were observed: Rhino virus 47.4 %, Myxovirus 26.3 %, Enterovirus 10.5 % and others 15.8 %.

These daily observed virus incidence frequences of upper respiratory infections, in relation to meteorological conditions, are similar to those reported by Sargent in the USA. An increase in incidence of upper respiratory infections was associated with cold front passages or the following peak of high barometric pressure. In further studies it was found that the cold front passages should occur during a period when the daily minimum temperature was below 0 °C and the barometric pressure was more than 1030 mbar. During cold front passages the temperature was falling distinctly and effected the respiratory system of man.

However, the effect of cooling does not depend only on temperature but also on air velocity and solar radiation.

The experience of cold (the so-called *Cold Degree*) can be determined with the following empirical formula:

$$y_1 = 0.013x_1 - 0.335x_2 + 0.142x_3 + 1.209 \qquad (1)$$

$$y_2 = 0.015x_1 - 0.306x_2 + 0.880 \qquad (2)$$

where, x_1 = temperature (°C); x_2 = air velocity (m/s); x_3 = solar radiation (cal/min/cm^2); y_1 = the time needed for water to fall in temperature from 37 °C to 27 °C; y_2 = the time needed for water to fall in temperature from 37 °C to 30 °C. The reciprocal value of y_1 or $y_2 \times 100$ represents the *Cold Degree index*.

Experiments with Chinese volunteers, during constant temperature, confirmed previous publications in the USA and Europe that also Chinese volunteers feel colder when air velocity is increasing and the nose temperature falls (Fig. 1).

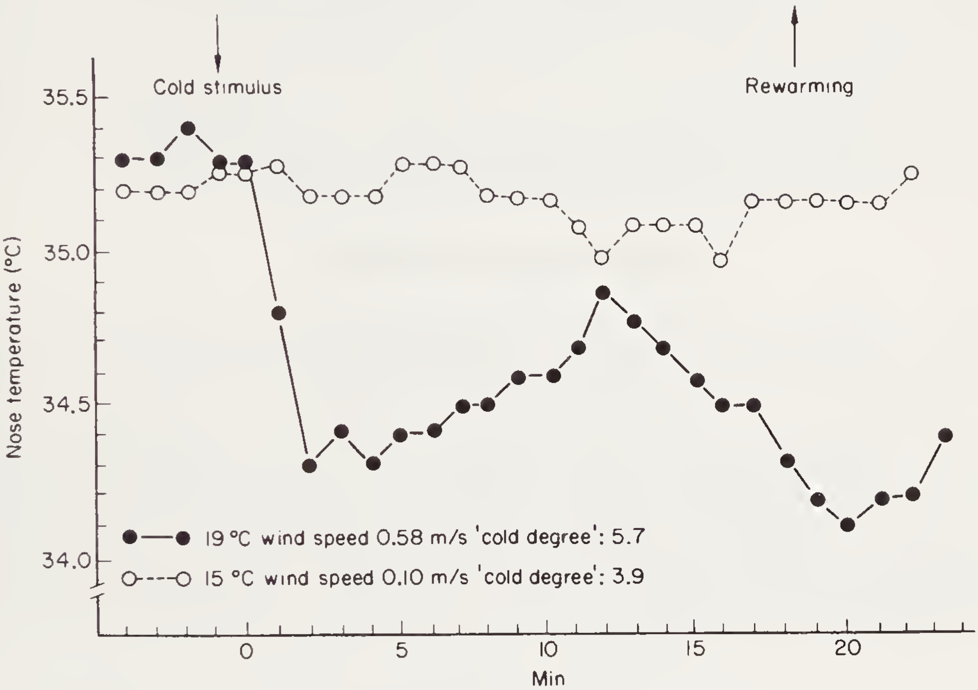

Fig. 1. Changes of nose temperature under different 'cold degree'.

When the nose temperature is falling the secretion of antibody (sIgA) may decrease. This was shown experimentally in seven healthy volunteers. The sIgA content in nose secretion of 7 volunteers is falling after they entered a cold environment. The sIgA mean value is 96.2 μg/100 mg total protein at 15 °C room temperature; after staying in a cold environment at −10 °C for 30 min the mean value drops to 42.3 μg/100 mg total protein ($t = 2.69, p < 0.05$).

Both our experimental and statistical studies indicate that a sudden drop in temperature forms the main trigger in upper respiratory infections. If the daily minimum temperature falls below 0 °C, the incidence of upper respiratory infections is rising. If this fall in daily minimum temperature below 0 °C continues, the incidence does not rise any more but sometimes even decreases. The same is observed if the monthly average temperature in November and December in Heilungkiang province falls below −10 °C.

Suppose the incidence of upper respiratory infections in November and December is given the value 100. If the monthly mean temperature in January and February falls to −17.7 °C, the incidence of upper respiratory injections falls to the value 60. A *modified water-bath test* of a group of volunteers seems to explain the thermoregulatory adaptation. If the hands of the volunteers are put into cold water in the month of October the nose temperature will drop 2 °C and rewarms after 20 min. The same person tested with the same method in the month of November shows a drop in nose temperature of only 0.6 °C and rewarms after 13 min. In February of the next year the nose temperature falls only 0.2 °C and rewarms already after 8 min. These observations indicate man's capacity to acclimatize to cold. This suggests that physical training of the cold resistance of a subject is recommended for people suffering from respiratory diseases.

BRONCHIAL ASTHMA

In Shanghai attacks of bronchial asthma always occur in spring and autumn. Daily observations in April–June and September–November 1975 and 1976, showed that asthma attacks in autumn are more frequent than in spring. Therefore it is unlikely that asthma is only caused by allergens. A regressive analysis of the data indicated that the frequency of asthma attacks in China is highest in spring or autumn when the average daily temperature is about 21 °C, the average temperature during the period of transition between spring and summer, and summer and autumn.

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The Influence of Weather on Rheumatoid Arthritis

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INTRODUCTION

The study of the influence of weather on rheumatic diseases is an important topic. Tromp (1977) compiled recent observations of the effects of weather and climate on rheumatic diseases. In the report he pointed out four meteorotropic physiological effects. In other publications Pilger (1970), Lawrence (1977) and Dirnagl, Kleinschmidt and Drexel, (1978) have summarized all reports known at present on this subject with respect to medical treatment.

The meteorological parameters which are known to aggravate rheumatic diseases do not give a homogenous impression of weather biotropy. This is not surprising if we consider the spatial and temporal inhomogeneity of the experimental data and the differences in clinical diagnosis (Dirnagl *et al.*, 1978). Beyond that, inadequate meteorological methods of analysis were often used, for example singular elements (humidity, air pressure, etc.) have only been examined (see in above mentioned publications).

The following investigation refers to the inflammatory attacks of rheumatoid arthritis (RA) in relation to the synoptic-scale weather processes. Therefore, in this study the bioclimatological aspects are not treated.

CLINICAL DATA

At the 'Clinic for External Therapy' in Bad Endbach near Frankfurt, West Germany (Medical Director: Dr. U. Storck) information was gathered during the period August 1971–September 1975. 100 fixed days of 123 acute inflammatory attacks were noted by patients suffering from RA (more than one attack per day has been treated statistically as only one). These data seemed to be very suitable for biometeorological evaluation as: (a) only stationary patients with RA have been selected; (b) only the first day of an attack after a longer resting phase has been recorded; (c) every inflammatory attack has been diagnosed by a physician by means of criteria e.g. swelling and warming up of the joints, decrease of mobility or blood tests. It should be pointed out that the usual arthritic irritation symptoms in joints have not been regarded; (d) no corticosteroid drugs have been used in the therapy because an important part of the medical treatment was physical therapy together with dietetic nutrition.

The patients, living mainly in the northern, northwestern or central parts of Germany stayed about 8–14 weeks at the hospital in Bad Endbach. About twenty patients were under observation. The fixed day, *N*, of an inflammatory attack has been defined as, that day on which a patient noticed symptoms in a joint for the first time or after a longer period of inactivity of the rheumatic process.

METEOROLOGICAL DATA

The biosynoptical analysis of the weather situations has been made according to the *bioclimogram* (Becker, 1962). The type of weather (Hess and Brezowsky, 1969), the air masses near the ground level (up to about 3000 m) and above (up to about 8000 m) after Scherhag's (1948) classification and the dynamic processes after the *Königsteiner Schema* (Becker, 1956) had been derived particularly from the daily weather charts prepared by the German Weather Service. In addition, meteorological observations of air temperature and humidity, the number of thunderstorms, front passages etc. were made close to Bad Endbach. The daily hygrograms referring to a special feature i.e. the nocturnal decrease of air-humidity were of great interest. This indicates a disturbance of the meteorological ground-level-conditions, seemingly a good indicator for the vertical turbulent exchange (Sönning, 1974).

STATISTICAL METHODS

The distributions of the meteorological parameters on the fixed days *N* had to be compared with those of all the other days by computing t- and χ^2-tests. In a similar way the meteorological conditions of the days before and after the fixed days N (from $N \pm 1$ to $N \pm 3$) were examined.*

*Details of the t-test of Von Schelling and the N-test of Ortman, Düll, Gundel and Hoelper were described in *Medical Biometeorology* (ed. S.W. Tromp). Elsevier Publ. Co., Amsterdam, 1963, pp. 176–178.

CONCLUSIONS

This statistical analysis showed a number of correlations. All were based on a significance level, $p < 0.05$. In the central area of W. Germany the following significant correlations were found between the frequency of particular weather conditions and the N-days with rheumatic complaint: (a) advection of warm air masses is reduced; (b) weather conditions caused by advection of cold (maritime) air masses are increased and according to that (c) upper-air up-and down-sliding motions are reduced; (d) vertical turbulent motions are highly increased.

Thunderstorms close to Bad Endbach were observed significantly more on the fixed N-days than on the average.

DISCUSSION

These conclusions do not contradict the results of other authors. Flach (1938) has pointed out already the coincidence of downward turbulent air flows with rheumatic pains. Beyond that, it was known previously that cold moist air is unfavourable to rheumatic diseases. The close relationship between thunderstorms and fixed N-days might point to the spherics-activity as one biotropic factor, but perhaps the spherics are only suitable as indicators for particular biotropic weather conditions and not as causal factor in rheumatic pains. Nevertheless the knowledge of the stochastic relations legitimate to include rheumatoid arthritis in the daily 'medical weather forecast' issued by the German Weather Service (Reinke and Swantes, 1978).

Further advances especially with respect to the mechanisms involved can only be expected from an interdisciplinary cooperation of rheumatologists, physiologists and meteorologists. Even with the above cooperation, it is stressed that standardized methods should always be used in the analysis of both biometeorological data and differentiated clinical data.

Editor's Note: In both *Medical Biometeorology*, 1963, and *Progress in Human Biometeorology*, 1977, (ed. S.W. Tromp), the reported meteorotropic effects of thunderstorms seem to be related to the heat-humidity stress during the oppressive weather conditions that precede most thunderstorms; these effects cause a disturbance of the heat regulation of subjects with malfunctioning thermoregulatory system (most frequently in old people and children).

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Season, Climate and Geographical Variation in Diabetic Prevalence

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In an earlier review (Wise, 1977a), it was concluded that variation in diabetes prevalence between different geographic areas was dependent on both environmental and genetic factors, with food intake being a particularly critical variable.

It was further claimed that the association of high diabetes prevalence with certain races (Pima Indian, Australian Aboriginal) and animal species (*Psammomys obesus, Ctenomys talarum, Acomys cahirinus*) which were currently or had previously inhabited warm and arid locations was not coincidental. Furthermore, a survival advantage of the diabetic genotype could be defined, manifest by an ability to withstand high environmental temperature, and subsist on a low energy requirement.

These linked phenomena can be related to a low resting metabolism, now clearly defined for Acomys (Wise, 1977a) and the Australian Aboriginal (Hammel *et al.,* 1959), but not yet examined in sufficient detail in the other high prevalence groups.

Since this review, additional evidence has accrued to support this basic tenet. The mutant obese-hyperglycaemic mouse in its homozygous form (ob/ob) also has a defect in thermogenesis permitting hypothermia and death to develop in an environmental temperature of 4 °C, and conversely maintaining a lower body temperature than lean heterozygotes at ambient temperatures of 30 °C (Trayhurn and James, 1978). That this is in fact genetic and not secondary to the obesity is shown by oxygen consumption experiments in weanling rats before obesity itself has developed, and where this thermoregulatory anomaly can already be demonstrated (Trayhurn *et al.,* 1977).

Collectively, these phenomena may explain why the Eskimo (in sharp contrast to a number of North American Indian groups), even in his present more urbanised existence, has a very low prevalence of diabetes; conceivably this may be based on the fact that selection for a diabetic genotype providing protection against environmental heat would not have been operative during evolution of that race.

Of interest once again in the human setting, is the long recognized syndrome of accidental hypothermia, occurring particularly following cold exposure in the elderly during winter months (Collins *et al.*, 1977). Recently, a concurrence of accidental hypothermia with hyperglycaemia has been documented purely as a clinical association (Gale and Tattersall, 1978). Although it was claimed by these authors that hypothermia itself impairs glucose utilization, and hence induced the hyperglycaemia, the reverse association has not been given sufficient attention. Thus proneness to 'accidental' hypothermia may itself be a feature of either clinical or subclinical diabetes mellitus, in a parallel situation to the sequence referred to above in the ob/ob mouse, and as similarly described in the spiny mouse (Wise, 1977b and c) and earlier in the Alloxan-diabetic rat (Berti, 1963). Further studies are clearly required in this area.

Turning to environmental factors which may determine seasonal or climatic variation in diabetes prevalence, a substantial body of information has accumulated to suggest that viral infection may have a significant role to play in either the precipitation or the primary genesis of juvenile-onset, insulin-requiring diabetes.

As long ago as 1926, Adams, in a series of 1000 diabetics in Minnesota, USA, showed a significant trend towards a September peak of new diabetic cases, with a lower incidence in May and June. This September peak was confirmed in a Finnish study by Somersalo *et al.* (1969). A further 2800 juvenile-onset type diabetics more recently analysed in the United Kingdom for seasonal onset (Gamble and Taylor, 1969), showed a minimum incidence in July-August and a significant maximum in November, the winter incidence of school aged children being three times that in the summer. It is interesting that MacMillan *et al.* (1977) also confirmed a major difference in incidence between winter (high) and summer (low) months in Kentucky, USA, but with significant trends restricted to school age (over 6 years) children. A British study (Bloom *et al.*, 1975) also failed to show any seasonal differences in the under-5 age group, while confirming the winter peak in older children.

The mechanism of these undoubted seasonal fluctuations remains to be fully clarified, but a number of possibilities may be considered.

Proneness to respiratory infections and diminished activity in the winter months are obvious possibilities. Since it has also been demonstrated that there are age-incidence peaks at 5–6 years, 12–13 years and less impressively at 17–18 years, conforming to periods of school entry, primary-secondary and secondary-tertiary education steps (Christau *et al.*, 1977), it could be suggested that stress may play an important role. Yet the possibility of exposure to viral infection (known to be associated with changes in school location) might explain both the age and the seasonal phenomena referred to above, and clearly deserves further attention.

Gamble *et al.* (1969) initially drew attention to the higher incidence of Coxsackie B4 virus antibody titres in patients with insulin-dependent diabetes of recent onset, and a lack of any significant serological evidence of respiratory virus infection in this same group of patients. More recently, the same group of workers (Coleman *et al.*, 1973) have demonstrated the ability of Coxsackie B4 to induce a diabetic syndrome in mice, approximately twelve days after infection, with characteristic β-cell changes. Other viruses may also be involved. In animals, the diabetogenic effect of foot-and-mouth disease virus, encephalomyocarditis (EMC) virus, and in humans the rubella virus have been well established, and further clarification of the role of infectious agents is likely in the near future.

Some recently reported studies in the Antarctic also deserve mention (Campbell *et al.*, 1975). Glucose tolerance tests, together with serum insulin and growth hormone responses were studied repeatedly in twelve normal subjects with a view to evaluating both diurnal as well as seasonal differences. Daily diet, periods of pre-test fasting and weights remained constant throughout the studies. However, there was a tendency to slightly higher activity in the summer months, and facilitated by the 24-h sunlight for 3 months of the year.

Blood glucose levels were significantly higher in winter months, suggesting that the hypoglycaemic effect of activity in summer months may have been relevant to these changes.

In the clinical setting, it may well be that the relative inactivity of winter may have been underestimated as a factor capable of precipitating diabetes; it has been well established that physical exercise has a very specific effect on increasing glucose utilization and perhaps to a greater extent in diabetics than in non-diabetics.

Finally, seasonal changes in endocrine pancreas and blood glucose have been quite extensively studied in animals and birds. Data has accumulated in throughbred horses (Gill *et al.*, 1974), Polish primitive horses (Gill *et al.*, 1977) and in a wide variety of migratory (Ljunggren, 1969) and domestic birds (Guha, 1977). Conflicting temperature-season responses are presented by these workers, and it is likely that endocrine (breeding) activity may represent additional complicating factors in these species.

In summary, evidence has been presented to support both genetic and environmental factors in determining significant differences in glucose metabolism and diabetes prevalence between seasonal and climatic extremes. It is likely that genetic predisposition to diabetes may be based specifically on a genotype selecting positively for high environmental temperatures and negatively for low environmental temperatures, a phenomenon which may explain some of the major differences in geographic prevalence rates both in animals and man.

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Observations on Possible Relationships Between Blood-Glucose Fluctuations in Insulin-Dependent Diabetics and Meteorological Parameters

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INTRODUCTION

If a study is made of the mean blood-glucose levels in a large population of insulin dependent juvenile diabetics who strictly adhere to diet and other relevant precepts obligatory for this disease, many unexplainable fluctuations in their condition are nevertheless observed. Preliminary studies during several years in a group of children living under the above mentioned regimen, revealed a reproducable pattern of blood-glucose dependence on meteorological conditions.

An increase of blood-glucose (BG) is associated with south-west weather situations, this type of weather includes upslide motion of subtropical air or anticyclonic east situations with downslide motion and advection of warm air masses. On the other hand a coincidence of decreasing blood-glucose and anticyclonic weather with moderate cold air and subsidence has been found (Jendritzky and Winkler, 1978).

One should particularly expect increased effects on some physiological parameters by exogenous factors, e.g. atmospheric stress exerted on the diabetics, because of their partly deficient homeostatic mechanisms. It would, therefore, seem justifiable to undertake a more extended study of the relationship of BG-fluctuations to weather conditions.*

*A discussion of the methods and results in greater detail has been published (Jendritzky and Winkler, 1979).

METHODOLOGY

Clinical methods

A group of 50–80 diabetic children and juveniles was studied for two years at a nursery home located at 860 m above sea level (between the Black Forest and Lake Constance). Their blood-glucose (BG) values were compared with the meteorological data of a nearby (20 km distance, 990 m altitude) meteorological station. BG-values taken at about 07.00 h*, three times a week, were used for statistical calculations; therefore possible biological rhythm effects could be ruled out as only meteorological data during the same hour in the morning were used. Blood glucose has been assayed with the GOD-Perid method (Werner, Ray and Wielinger, 1970). Time-series of blood-glucose fluctuations include different bands of frequencies, but for biosynoptical analysis only fluctuations with a characteristic time-scale of one day are of interest. The desired separation of frequencies has been obtained by numerical filtering. To the left, Fig. 1 shows the low frequency variations (LF) and to the right the high frequency (HF) with apparently irregular fluctuations around the average.

Meteorological methods

The short-term aperiodic variations of weather were determined by the sum of fluctuations of different meteorological variables (Brezowsky, 1963; Ungeheuer and Brezowsky, 1965). Former attempts to determine a single factor of 'biotropy' to define all the observed biometeorotropic phenomena were bound to be unsuccessful, because the effect of weather depends on a meteorological accord. The influence of weather in closed or air-conditioned rooms is remarkable, indicating that the atmospheric conditions near the ground are only able to represent a limited part of the problem of biotropy (Richner, 1974).

Short-period variations of weather e.g. the passage of a front with a change in the air-mass, are closely linked to temperature-humidity variations (Ungeheuer and Brezowsky, 1965), which additionally include information of some other meteorological elements (Brezowsky, 1963). The state of the temperature-humidity environment (THE) has often been used as an indicator of changes in general tropospheric conditions. In this way the actual temperature and humidity data on a fixed day have to be compared to the past meteorological data. This is obtained by computation of weighted means of the corresponding data of the past, e.g. seven days (Dirnagl, 1977). The deviations of the following temperature-humidity conditions are of particular interest: warmer and more humid, cooler and less humid,

*The technical assistance of Mrs. B. Schmutz and Miss B. Wägele is gratefully acknowledged.

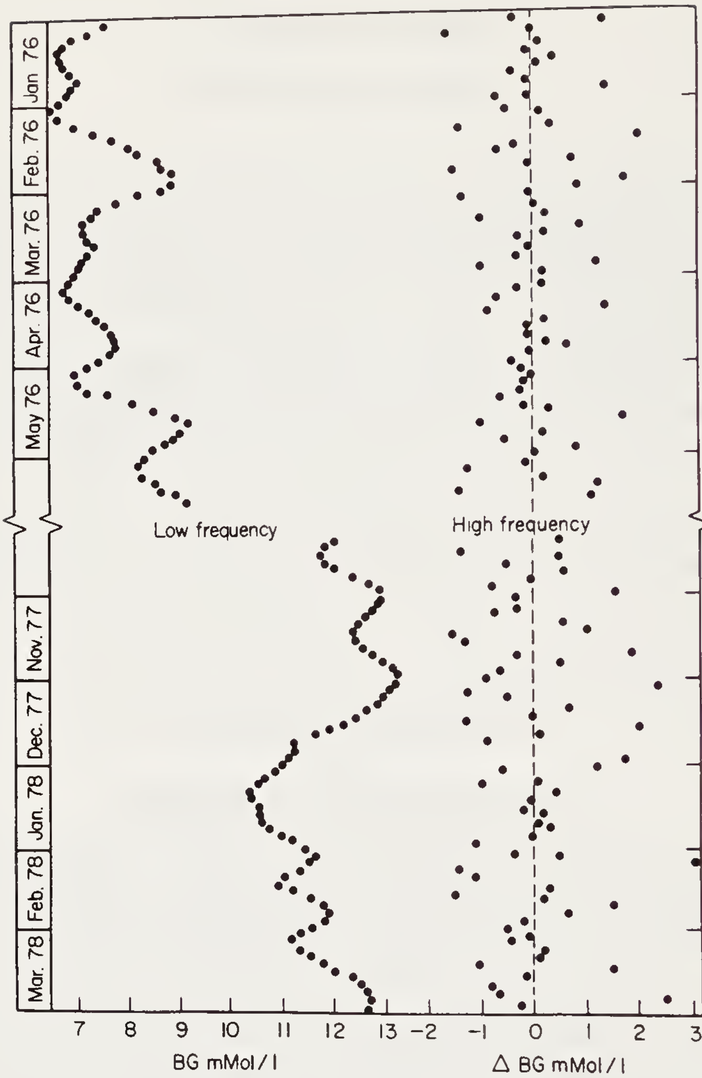

Fig. 1. Time-series of fluctuations of blood-glucose (detail). Discrimination in low- and high-frequency parts.

relative to the conditions in the past in each case. The former deviation is indicative of a weather situation of increasing cyclonality, advection of warm air (often subtropical air masses) and upslide motion. The latter is linked to a general calming down of the weather, large scale subsidence and development of a new anticyclone.

Obviously this simple scheme will not be able to describe all the weather situations which may occur, nevertheless the temperature-humidity environment is an useful procedure to study the relations of weather and biological processes.

RESULTS

Synchronization of the mentioned series of BG-values with meteorological influence is best represented in the case of correlation of BG-values to the two opposite classes of the temperature-humidity environment in Fig. 2.

A change in the environment to warmer and more humid conditions, indicating the beginning of advection of warm air masses, i.e. increasing cyclonality, have been connected with an elevation of BG-values, an over-proportionate rise relative to the changes in the meteorological parameters. Similar reaction is observed in the BG-values with a reversal in the weather i.e. if the temperature-humidity environment turns colder and less humid which is connected, with increasing anticyclonality.

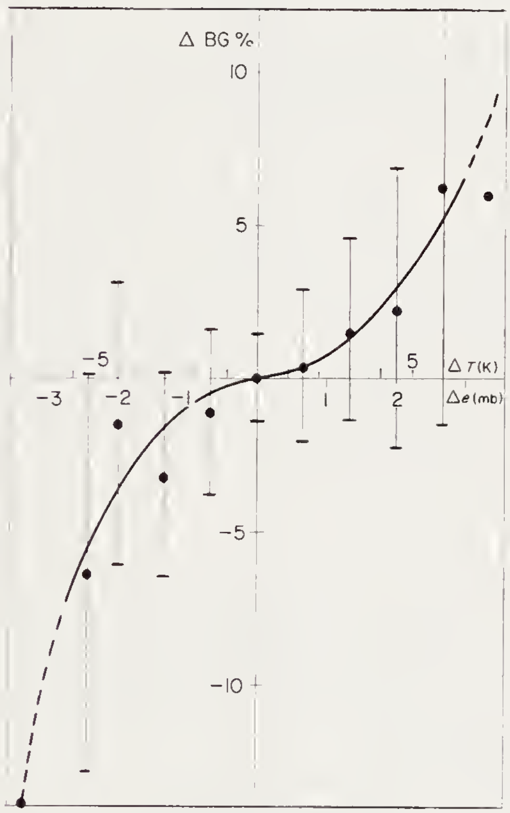

Fig. 2 Variation of blood-glucose (BG) as a function of changes in the temperature-humidity environment (THE). Confidence intervals at the 5% level of significance.

DISCUSSION

A review of previously published reports suggest some contradictions to the above results e.g. the report by Menger and Pahl (1960). These discrepancies may be explained by the use of different laboratory methods, by the use of different experimental parameters (blood-glucose/urinary-glucose) and by correlations with noncomparable meteorological conditions. During the period of observation of Menger and Pahl, NW Germany was dominated by cyclonic weather conditions. These conditions would have effectively increased the BG-values with regard to our results, because at the beginning of cyclonal weather i.e. the change of the temperature-humidity environment to warmer and more humid conditions, is associated with increasing blood-glucose. Lower BG-values are expected by development of an anticyclone with only low cooling power in spite of the still relatively cold air.

Some experiments with animals (Brezowsky and Hansen, 1961) show, when compared to our results, the same changes in BG-values of starved non-diabetic rabbits, but completely opposite relations in the case of well fed rabbits. Crecelius and Warmbt (1957) have worked out the importance of a total tropospheric cooling during periods of increased glucose excretion in urine.

Wise (1977) stresses the importance of diet as an essential determinant of blood-glucose fluctuations. This is most valid in the case of infantile and juvenile diabetes, because there is little chance of endogenous regulations as result of insufficient insulin secretion. Tromp commented on this statement and raised the following question: Why should one not accept the idea of thermal stress on the whole organism, as, influences of this kind on the function of liver and pancreas have been verified so far? Apart from the effects of catecholamines and corticosteroids as classical 'stress hormones', due to their regulatory properties over glucogenesis, it should be kept in mind that more potent than these two hormones is glucagon. Glucagon, which is secreted from the pancreas, is still effective in the diabetic, and may be relevant to the mechanism discussed by Tromp.

Moreover it should also be noted that a slight improvement of the metabolic condition can occur during more frequent outdoor activities of children (Winkler, Heinze and Proetzsch, 1978) and (Zinman *et al.* 1977) during fair weather conditions (temperature-humidity environment becomes cooler and less humid) due to an increased absorbtion of insulin at the site of injection.

CONCLUSION

In accordance with earlier reports there can be no doubt of a correlation between metabolic state and the meteorological component of exogenous influences. This is particularly applicable to diabetics i.e. in the fluctuations of blood-glucose levels.

This can be defined as a reaction of the body to the 'biometeorological accord' acting consistently, although not yet explicable. Further investigations into the frequency of hypoglycemic reactions should help to clarify the remaining unsolved questions leading to the eventual improvement of the therapeutics of diabetes.

Acknowledgement

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Observations of the Influence of Weather and Climate upon Microbial Survival and Spread of Disease by Aerosols

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INTRODUCTION

This article highlights observations (made during the last decade) concerning the survival and spread of microorganisms by aerosols. For a more complete account of effects of this and other stresses upon microbes, the reader is referred to the following: Dimmick and Akers, 1969; Silver, 1970; Nilsson, 1973; Calpouzos and Campos, 1973; Commission C1, 1973; Hers and Winkler, 1973; Gray and Postgate, 1976; Donaldson, 1978.

FACTORS AFFECTING SURVIVAL AND INFECTIVITY OF MICROORGANISMS

Open air factor

An important discovery was made by Druett and May (1968), who found that open (or outside) air contains components which, at extremely low concentrations, can kill airborne microorganisms. These components, termed the Open Air Factor (OAF), vary in concentration at a given location, are ephemeral and are therefore difficult to preserve in containers. Studies of the action of OAF indicate that only spores are likely to be resistant to it, although, unless the concentration of OAF is high, the rate of loss of viability (thence infectivity) of other microbes in the airborne state is not so rapid that they are all killed within a few minutes. Therefore, marked effects of OAF *per se* are usually apparent only when the airborne state is maintained for 20 min or longer. On the other hand, in indoor conditions, little or no effect of OAF would be anticipated, unless well ventilated conditions applied, such that OAF is replenished continuously by air drawn in from outside.

It was suspected fairly early in the studies of OAF that the factor resulted from reactions between ozone and olefins. Attempts to detect and identify OAF by chemical means, or by long path infrared studies, failed, probably because OAF occurs at such low concentrations. Nevertheless, using the loss of viability of *Escherichia coli* induced by OAF together with equations derived by Cox *et al.*, it was possible to obtain relative concentrations of OAF. Such values were correlated by De Mik and De Groot (1977a–c) with concentrations of various pollutants e.g. for ozone, $r = 0.90$; for C_3H_6, $r = 0.61$, while for oxides of nitrogen, sulphur dioxide, ethylene, acetylene etc., much lower, or even negative correlation coefficients were obtained.

Other work by De Mik and De Groot, and also Druett and Nash (Druett and May, 1969; Druett, 1973; Nash, 1973), showed that synthetic OAF can be produced by reacting together very low concentrations (pphm) of ozone with olefins. Synthetic OAF, as with the 'outside' version, is both bactericidal and viricidal and can cause protein and DNA damage. As a consequence, introduction of synthetic OAF into e.g. hospital suites, might decrease levels of contamination by viable microorganisms. Since animals and man in the open air are exposed to OAF, such a procedure would not be expected to cause an increased health hazard due to artificial OAF *per se*, unless it is present at high concentration.

Summarizing the effects of OAF, the spread of disease by the airborne route depends upon the nature of the microorganism, the prevailing OAF concentration, time airborne, wind speed and trajectory, the nature and level of pollutants, ozone concentration, height of inversion layer (if present), temperature, relative humidity and time of day.

Oxygen

Another atmospheric component which can cause loss of viability of some bacteria (but not bacteriophages or viruses) as aerosols or dry powders, is oxygen. Its lethality depends upon its concentration, the relative humidity and exposure time, as well as the nature of the bacterium. A mathematical model which accounts extremely well for these effects has been derived by Cox *et al.* References to this, and earlier work, and discussion of the possible involvement of free radicals in the phenomenon, may be found in the review by Strange and Cox (1976). This review also discusses the evidence which indicates that, at least for *Escherichia coli B*, oxygen is toxic because it causes an inhibition of cell division.

Air pressure changes

Included in the proceedings of the IVth International Symposium on Aerobiology (mistakenly called the VIth International Symposium on

Aerobiology on its title page) edited by Hers and Winkler (1973), is a paper by Druett on effects of rapid expansion and recompression of air upon survival. Under conditions which cause the condensation of water on, and re-evaporation from, aerosol particles, *Escherichia coli* (contained within the particles) was rapidly killed. Although the effect has not been investigated widely, it is likely that the resulting bacterial cell wall damage (and concomitant death) would occur also with other microorganisms.

Relative humidity

Studies of relative humidity (RH) effects have been in two main areas, namely, in RH changes before sampling and in detailed studies of how survival is influenced by storage RH. Several authors have found that gentle rehumidification (or rehydration) of aerosols immediately before collection usually results in enhanced survival of dried bacteria and phages. For bacteria, this process prevents or reverses damage to cell walls, while for certain phages it prevents shearing of phage tails from phage heads during collection.

These effects, which mimic events occurring naturally when aerosolized particles are inhaled, can depend upon the storage humidity, e.g. enhanced survival may occur only when the storage RH is less than 80%. The importance of the latter is greater than previous work indicated, because detailed studies of its influence have shown that survival can depend critically upon storage RH, especially in certain RH ranges. In addition, the critical range of RH resulting in poor survival is not necessarily the same for aerosols of microorganisms disseminated from the wet and dry states, i.e. at a given storage RH, the rate of loss of viability depends upon whether the aerosol is generated from a liquid suspension or from a dried powder. Therefore, even at a fixed storage RH, the aerosol stability of a given microbe can depend upon whether generation is by e.g. coughing, sneezing etc. or by disturbing dust etc. Consequently, generalizations previously made concerning the influence of RH upon aerosol stability should be treated with extreme caution.

Metabolism in aerosols

The possibility of e.g. bacteria metabolizing and dividing in the airborne state relates to the spread of infection on Earth, and to the contamination by space craft of the atmospheres of e.g. Jupiter or Saturn, and their satellites. Before 1975 there was no direct evidence that metabolic processes could occur in airborne microorganisms. Since then, Dimmick and co-workers (Dimmick *et al.*, 1975; Straat *et al.*, 1977) have shown that aerosolized *Serratia marcescens* (held in chambers at 30 °C and 95% RH) produce $^{14}CO_2$ from ^{14}C-labelled glucose, incorporate ^{3}H-thymidine into deoxyribonucleic acid and divide for at least two generations. It can be concluded, therefore, that under suitable conditions, *S. marcescens* can metabolize and divide in the airborne state. In the presence of OAF etc. the rate of induced loss of viability probably would be greater than the rate of growth, so that the net effect would be for the microbial population to die.

Repair of microorganisms

When populations of microorganisms are stressed some members may die, others may be injured, while the remainder may be apparently unaffected. The injured microbes may fail to grow under one set of conditions, but given a suitable environment are capable of complete recovery. Recent work indicates that the above is due to mechanisms for the repair of damage to membranes and nucleic acids. With bacteria, molecules ranging from ions, simple sugars and amino acids, to peptides can be essential for such repair to take place. As a consequence, the apparent ability of a population of a given microorganism to survive a stress depends upon whether or not the microorganism has mechanisms for the repair of the induced damage, and also whether or not these mechanisms are 'switched on'. So far, repair has only been demonstrated *in vitro*, but presumably it occurs also *in vivo*.

Other factors

In addition to the above factors, there are several others which influence survival, but since they have not been studied to any great extent during the last decade, they will not be discussed here. For convenience, the more important factors known to affect survival are listed below; their order is not intended to imply any ranking of significance, but rather to reflect the stages involved in aerosol generation, storage and recovery: (i) nature of the microorganism; (ii) conditions for growth; (iii) suspending medium; (iv) method of aerosol generation; (v) particle size distribution; (vi) storage relative humidity; (vii) temperature; (viii) pressure fluctuations; and finally (ix) open air factor (OAF) concentration.

For the spread of infection by the airborne route, the above are important as well as the infectivity of the microorganism. Factors affecting virulence *per se* have received very little attention so far, except for, perhaps, the influence of particle size and the discovery of virulence suppressors in natural fluids. The former is important because it determines the landing sites of the aerosol particles in the host, and therefore can affect the form of the disease, while the latter, such as chloride ions, can destroy virulence without concomitant loss of viability in aerosols.

CONCLUSION

The ability of a given microorganism to survive and to remain infective in the airborne state depends to a large extent upon environmental factors, therefore, weather and climate must play an extremely important role in airborne transmission of disease.

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Studies on the Mechanisms of Microbial Adaptation to the Physical Environment

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INTRODUCTION

The environmental factors which affect humans and other animals also influence the microorganisms which are such an important part of our ecology. Some of the microorganisms are very closely associated with animals, living in the digestive tract and synthesizing essential nutrients for the host. For these microbes, most external physical changes are of little consequence, because they are well shielded by the animals' homeostatic systems. The vast majority of microorganisms, however, live free in nature, especially in the soil and oceans. It has been estimated that the upper 15 cm of a fertile soil may contain over 4000 kg of bacteria and fungi per hectare (Stanier *et al.*, 1963). These organisms are responsible for degrading the complex molecules of plants and animals when they die, eventually producing simple organics, carbon dioxide, and inorganics, which are then used for the next cycle of plant growth. It is believed that over 90 % of the biologically produced carbon dioxide results from the metabolic activity of bacteria and fungi. In addition to recycling plant nutrients, soil bacteria also provide new nutrients through 'fixation' of atmospheric nitrogen into ammonia and nitrate, the forms which can be used by plants. Microorganisms also have an enormous capacity for detoxifying both natural and man-made poisons.

All of these functions of microorganisms are essential to the operation of the material cycles on Earth. This is true of all locations on the planet, regardless of the climate or other environmental factors. In fact, one of the most impressive attributes of microorganisms is their ability to adapt to every stable environment on Earth. These include such extremes as polar regions, hot springs, water saturated with salt, mountain tops, ocean depths, acid and alkaline waters, deserts, intense radioactivity, soil and water contaminated with toxic chemicals or petroleum, and areas devoid of oxygen. Microorganisms are also found suspended in the atmosphere, although it has not been possible to prove that they multiply there.

The conditions found in these environments are more severe than those we usually assume can be tolerated even by cell constitutents – the enzymes, nucleic acids, membranes, etc. The fact that organisms populate all those areas indicates that the structure of cell components can be modified to maintain function under severe environmental stress. These interesting organisms are ideal tools for studying those adaptations, and they have been used extensively in that way. Eventually it will be possible to correlate changes in molecular structure, cell structure, and metabolic pathways with the ability to adapt to particular physical parameters. This review will present some of the more recent work in those directions, including principally the effects of high temperature, low temperature, and pressure. Two recent books are useful references (Heinrich, 1976; Kushner, 1978).

ADAPTATION TO HIGH TEMPERATURE

Probably the most impressive adaptation is that of bacteria to high temperature, including strains living in hot springs, hot acid waters, home and industrial hot water heaters, and decomposing organic material (Tansey and Brock, 1978). Although spores are well known to have great heat resistance, most of these *thermophilic organisms* are not spore-formers, and the resistance is inherent to the vegetative cells. Bacteria are known to inhabit boiling springs (95 °C at that altitude), and their growth rate has been measured *in situ* (Bott and Brock, 1969). Other microorganisms are not as tolerant to heat as are bacteria; photosynthetic algae (*blue-green*) are found up to *c*. 70 °C, other algae and fungi up to 60 °C, and protozoa up to 56 °C (Tansey *et al.*, 1978). It should also be pointed out that, for all these organisms, there are many different strains, with different optimum and maximum growth temperatures.

It is obvious that thermophilic organisms must differ considerably from their more common mesophilic relatives. Among the required changes for life at high temperatures would be a stabilization of enzymes and nucleic acids, and an increase in the melting point of lipids. One possibility which has been considered is that thermophilic organisms contain stabilizing factors which prevent denaturation of their enzymes and nucleic acids. Although considerable effort has been spent in looking for enzyme stabilizers, it has not been possible to prove their existence. In fact, enzymes isolated from thermophiles, purified and repeatedly recrystallized, retain their heat resistance. Thus the stability of thermophilic enzymes appears to be an inherent property of the enzyme molecule. This provides an excellent opportunity to study the factors which contribute to protein stability, by comparing the structure of the same enzyme isolated from organisms which live at different temperatures. Prior work has been reviewed by Ljungdahl and Sherod (1976) and by Amelunxen and Murdock (1978). The stability of protein molecules may be influenced by changing the amino acid composition, or by changing the amino acid sequence. Changes of either kind will result in a protein with different charged groups, hydrophobic groups, hydrogen bonding, salt linkages, or disulfide bonds, and these will result in altered secondary structure (helicity, β-structure). Singleton (1976) made an extensive analysis of data for 12 enzymes isolated from 15 thermophilic and 56 non-thermophilic organisms. Although there were slight differences in the amino acid composition of the same enzyme of these two classes, there were no significant, consistent differences which were characteristic of thermophilic enzymes. Also, several calculated structural parameters (helix content, hydrophobicity index, melting point) did not show significant differences. The only property which showed a correlation was a decrease in the β-sheet content of most of the thermophilic enzymes. It is apparent that the heat stability of these proteins will not be explained by any of the obvious possibilities, but that detailed knowledge of sequence and 3-dimensional structure will be required.

One series of studies in that direction concerns *ferredoxin*, isolated from thermophilic and other *Clostridia* (Devanathan *et al.*, 1969). When these molecules were sequenced (Tanaka *et al.*, 1973), several differences were found; the net result of the amino acid substitutions shows thermophilic ferredoxins to have more charged groups and to be more acid. Adman, Sieker and Jensen (1973) determined the 3-dimensional structure of ferredoxin from *Micrococcus aerogenes* by X-ray diffraction; Tanaka *et al.* (1973) and Perutz and Raidt (1975) made a detailed analysis of *Clostridial* ferredoxins based on that model. They concluded, among other things, that the thermophilic ferredoxins were stabilized by salt bridges between residues near the ends of the molecule.

The ferredoxins are not ideal models for enzymes because they are only a fraction of the size, and have only limited secondary structure. Recently Harris' laboratory has reported the first complete sequence and structure (by X-ray diffraction) of a thermophilic enzyme, the glyceraldehyde 3-phosphate dehydrogenase from *Bacillus stearothermophilus* (Biesecker *et al.*, 1977). A detailed comparison with the mesophilic enzyme (from lobster muscle) shows a great deal of similarity, and some differences. An unexpected finding was that the core of the thermophilic enzyme was no more hydrophobic than that of the mesophilic enzyme. It appears that one of the principal factors in the stability of the thermophilic enzyme is its higher content of arginines, two of which form additional salt bridges between some of the four sub-units (of 333 amino acids each) which make up the active enzyme. Further study of this and other enzymes, as they become available, will provide more details about the factors contributing to stability. It is apparent now, however, that stability to heat is due to a summation of many subtle changes in the structure of the protein.

Nucleic acids are another class of macromolecules which are 'denatured' at high temperatures. In this case, heat destroys the hydrogen bonds which maintain the double helix of DNA and the complex RNA structures. These changes can be followed by measuring the increase in absorbance at 260 nm of a nucleic acid solution as it is heated; the mid-point of this curve is the transition or melting-out temperature, T_m. Not surprisingly, the nucleic acids of thermophilic organisms have T_m's as much as 20 °C higher than those of mesophiles (for reviews see Stenesh, 1976; Reid, 1976). With DNA, the stabilization can be accounted for largely by an increase in the guanine-plus-cytosine content, with their strong hydrogen bonding, and a corresponding decrease in adenine-plus-thymine. Transfer RNAs, with their modified (or 'minor') bases, offer further opportunities for stabilization, as found by Watanabe *et al.* (1974, 1976a) in *Thermus thermophilus*, which grows at 85 °C. This organism has methionine-transfer RNA with an extra guanine-cytosine pair, as compared with the very similar tRNA from *Escherichia coli.* Even more important, however, is the stabilization due to bonding with a new base (5-methyl-2-thiouridine), probably formed by addition of sulfur to the one ribothymidine in the RNA. In fact, the amount of thio-ribothymidine in the transfer RNA was proportional to the growth temperature, suggesting that a thiolating enzyme became more active as the temperature increased (Watanabe *et al.*, 1976b).

Although no external factors have been implicated in stabilizing thermophilic proteins, this may not be true for the nucleic acids. Oshima (1975), in studying the role of polyamines in high-temperature protein synthesis, isolated the amines from *T. thermophilus.* He found spermine and a new tetra-amine, $H(NH\,CH_2\,CH_2\,CH_2)_3\,NH_2$, which he called thermine. DeRosa *et al.* (1976) found spermidine, thermine, and a new triamine, $H(NH\,CH_2\,CH_2\,CH_2)_2\,NH_2$, which they named caldine, in *Caldariella acidophila.* These polyamines may well function to stabilize nucleic acids *in vivo*, as they are known to do *in vitro*.

Lipids of animals, plants, and microorganisms have long been known to vary in composition with the environmental temperature. This is another essential adaptation for thermophilic microbes, which would otherwise contain just a droplet of melted fat. Probably the most important function of the lipids is to maintain the integrity of the cell membranes, which are vital for structure, transport, and enzyme activity. The current view is that the organism must maintain the proper lipids so that the temperature of transition between the gel and liquid-crystalline states in the membrane lipids falls near the growth temperature (McElhaney, 1976; Esser and Souza, 1976). This is accomplished by varying the chain length, branching, and unsaturation in the fatty acids of the lipids. A more extreme change is described by DeRosa *et al.* (1977) and by Langworthy and Mayberry (1976) for thermophilic, acidophilic bacteria of the *Caldariella* group. Instead of the normal ester lipids, these organisms contain ether lipids based on a 72-member macrocyclic tetraether containing two C_{40} phytane diols plus glycerol and nonitol. The other major components of membranes, the proteins, are discussed by Welker (1976).

ADAPTATION TO LOW TEMPERATURE

The cold areas of the Earth include not only the polar regions and mountains, but also the greatest portion of the oceans. Living organisms are found in all these locations (Baross and Morita, 1978). As ZoBell (1962) has pointed out, more than 90% of ocean water is colder than 5 °C, and only a relatively thin layer at the surface varies in temperature with the climate. Nevertheless, microorganisms are found at all depths. Most of the investigation of the polar regions has been concentrated in the Antarctic, where every area studied has been found to contain organisms (Cameron *et al.* 1976; Uydess and Vishniac, 1976).

The organisms growing at low temperatures (*psychrophiles*) usually have their entire growth range shifted downward. Growth rates at lower temperatures (e.g. in the area of 0–15 °C, depending on the organism) are generally similar to those of mesophilic organisms at 25–30 °C. With both minimum and maximum growth temperatures changed, there is considerable study of just what factors set these limits (Inniss and Ingraham, 1978). It has been shown that protein synthesis, both *in vivo* and *in vitro*, is reduced when the temperature approaches the maximum. The same system appears to be limiting when tested at the minimum temperature for growth (Broeze *et al.*, 1978); specifically, initiation of translation is blocked, but it is possible that this is related to energy levels in the cell. Psychrophiles also show lipid and membrane changes, but in the direction opposite to those for thermophiles, of course. Some enzymes have been purified from psychrophiles, and shown to have activity at lower temperatures, but the studies have not reached the definition of those with thermophiles discussed above.

ADAPTATION TO PRESSURE

Microorganisms which are exposed to high pressures are found principally in the deep ocean (over 10 000 m; 1160 atm), and in deep oil and sulfur wells. Although there is no question that organisms live at those pressures, it is not certain that this represents a true adaptation, or that these so-called *barophiles* actually require higher pressures. Apparently many common bacteria grow better at somewhat higher pressures, depending also on other conditions. An example is *S. faecalis* 9790, which shows maximum growth rate at 100 atm. and 45 °C (Marquis and Matsumura, 1978). It is believed that microbial activity is low in deep waters, which are also cold, although measurements are difficult. High pressure will affect a chemical reaction which results in a change in volume. Among biochemical reactions at pressures found in nature, little change would be expected for most small molecule interactions, DNA is stabilized because its denaturation would result in a small increase in volume, and most proteins appear to be stabilized slightly.

CONCLUSIONS

From this brief summary, it is apparent that we have only the most elementary understanding of the molecular mechanisms by which microorganisms adapt to their environment. Studies of adaptation to high temperature have been the most popular, and have produced the most definitive results. It is evident now that these remarkable adjustments to physical factors are brought about by subtle changes in molecular architecture.

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The Influence of Season upon Type A Influenza

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INTRODUCTION

In the long course of evolution the fauna and flora of the earth have adapted in countless ways in order to use or to evade the hazards of the effects of seasonal variation on their living conditions (Woodbury 1954).

Seasonal infectious diseases are no exception to the general law that every process on earth with a seasonal rhythm is directly, or indirectly, under the influence of changes in intensity and composition of solar radiation. The mechanism by which the solar influence is mediated may be recognizable, as in diseases transmitted by insect vectors, but in many seasonal diseases the intermediate mechanisms are as yet unidentified.

There are two simple types of evidence that show that a disease is controlled by seasonal influence. First, it recurs more or less at the same season at locations in the same latitude. Second, outbreaks south of the tropic of Capricorn succeed or precede those north of the tropic of Cancer by up to six months. The present paper gives examples illustrating both sorts of evidence for 'type A' epidemic influenza. Readers wishing to study the evidence in greater depth are advised to read successive issues of the Weekly Epidemiological Record of the World Health Organisation (WHO), the Weekly Communicable Disease Report (CDR) for England and Wales, and the following references: Davignon and Williams (1974); Delon and Assaad (1976); Foy, Cooney and Allan (1976); Hopken *et al.* (1977); Hosny *et al.* (1972); Ivan and Duda (1976); Madai (1975); Marine, McGowan and Thomas (1976), Medical Superintendent's Annual Reports of Fairfield Hospital, Melbourne, Australia; Pereira and Chakraverty (1974); Strnad *et al.* (1976); Werner, Shudrowitz and Kohler (1975). Similar evidence of seasonality is adduced for the causal parasite, influenza A virus, and for seasonal influence on the intimacies of its antigenic variations. An unexpected synchronicity between longer-term cyclic changes in both solar activity and influenzal epidemic behaviour is mentioned.

Influenza is currently believed to survive and propagate by simple direct spread from case to case, a hypothesis that takes no account of seasonality and leaves unexplained most of the major features observed in the epidemic behaviour of the disease. An alternative hypothesis which suggests the role of the unidentified seasonal influence is therefore discussed.

Some infectious diseases prefer the warmer months, some the colder months and some are indifferent to season. Five common respiratory viruses were most prevalent in the colder months in a five-year surveillance of a small population in Cirencester, England, namely: influenza A and B viruses, parainfluenza viruses of types 1 and 2, and respiratory syncytial virus (Hope-Simpson and Higgins, 1969). Type 3 parainfluenza virus showed a high cold-season prevalence in addition to a peak in late summer. These six viruses are structurally and chemically akin — *myxoviruses* of helical symmetry, possessing RNA, ether-labile and coated with a limiting membrane. The common viruses found to have a warm-season preference or to be evenly distributed throughout the year differ in important respects from the cold-season group: *herpes virus hominis* and *adenoviruses* contain DNA, are of icosahedral symmetry and are ether-stable, and *coxsackieviruses* and *rhinoviruses* possess RNA but are ether-stable and lack a membrane. Base-sequence analysis has shown that the two influenza viruses could have descended from a common ancester, so perhaps the members of the cold-season *myxovirus* group all inherit somewhere in their physico-chemical make-up the same adaptation that responds to the unidentified cold-seasonal influence. Alternatively the similar behaviour may result from convergent evolution.

Influenza A virus was the most consistently cold-seasonal of the group. The phrase 'cold-seasonal' may mislead us into confusing climatic with seasonal influences. The investigation was carried out in a northern temperate climate at latitude 53 °N, but type A influenza is remarkably little affected by influences that determine the epidemic behaviour of most other infectious diseases. It breaks out in all inhabited parts of the globe irrespective of climate, temperature, rainfall, altitude, latitude, longitude, race and sex. In the tropics it cannot be considered a cold-season disease. Yet the influence of season alone exerts overall control, determining when influenza will appear in a particular locality, the sequence in which it appears at different latitudes proclaiming clearly the influence of agencies dependent, positively or negatively, on solar radiation.

SEASONALITY OF INFLUENZA EPIDEMICS

Even in an area as small as the United Kingdom of Great Britain (UK) latitude can be seen to determine the timing of the harvest and the ripening of fruit from south to north. Influenza epidemics are more variable both as to timing and as to their duration, and the differential effect of latitude is most readily appreciated on the global scale. North of the tropic of Cancer outbreaks occur in the northern hemisphere's colder months between October and March whereas south of the tropic of Capricorn they tend to occur in the southern hemisphere's colder months between April and September. Tropical areas between Cancer and Capricorn have their epidemics in the rainy monsoons. Figure 1, showing the timing of influenza epidemics on the African continent, depicts the phenomenon of the effect of latitude, giving the misleading impression that the disease was travelling by chains of direct transmissions from the Union of South Africa (latitude 30 °S) at the southernmost extremity of the continent in May 1950 via the tropical states to reach the northern states on the Mediterranean shore (latitude 30—39 °N) by January to March 1951. The regular repetition of this and similar sequences (see Fig. 4) signifies, as with crops, leaf-fall and all other such processes, the movement of the seasonal influence across the face of the earth as its position shifts in relation to the sun.

An example of influenza seasonality in a small population is shown by a long-term viral surveillance in Cirencester, England (latitude 53 °N). Figure 2 shows *'Hong-Kong' influenza* virus reaching the area for the first time in mid-January 1969. It caused such a small outbreak, despite

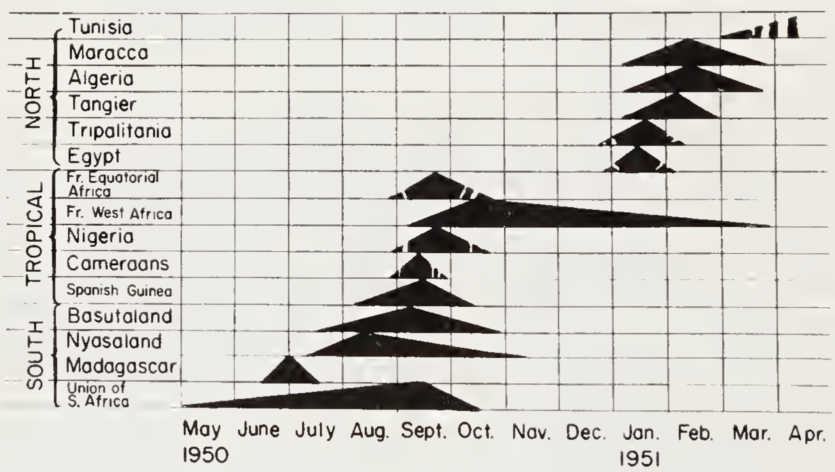

Fig. 1. Influenza epidemics in Africa, May 1950 to April 1951, to show how a seasonal influence determined the timing of epidemics from S to N across the continent, so creating the misleading impression that the disease was travelling by direct spread. (Figure constructed in 1951 from records in the influenza department of WHO by courtesy of Drs Freyche and Klimt).

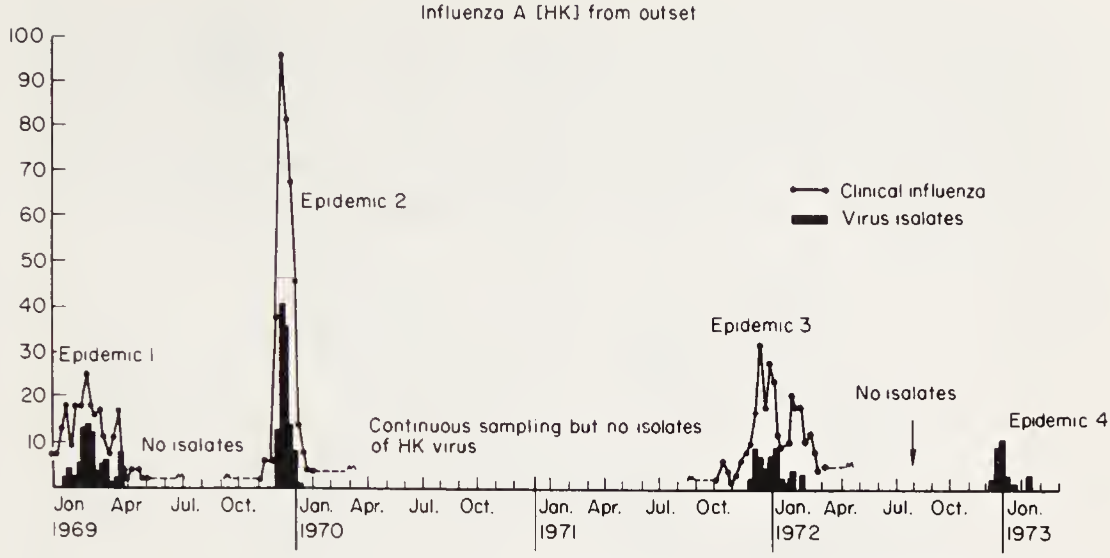

Fig. 2. The first epidemics caused by H_3N_2 influenza A virus in a general practice population, to show the seasonality of the disease and of the virus in a single small location. (From a clinical and virological surveillance in Cirencester, England.)

the population's lack of any previous experience of the virus, that 95% had escaped attack when the epidemic terminated on 15th April 1969. Why did the epidemic cease in a situation so favourable for continued spread? No influenza virus could be found for the next eight months, but the popular explanation that the epidemic had been stopped by subclinical infections immunising the community was dramatically dispelled when a second *'Hong Kong' influenza* A epidemic erupted simultaneously over a wide area in early December 1969. This severe second epidemic stopped abruptly after less than six weeks leaving some 80% of the population still unattacked, and for nearly two years thereafter no further influenza A virus was found until a third epidemic of type A influenza occurred in the winter of 1971–72. The seasonality of these epidemics, with long periods of absence of the virus between them, was closely paralleled in many other localities in northern latitudes, as illustrated by the comparison of morbidity data from Cirencester (latitude 53 °N, longitude 4 °W) and the Czech Socialist Republic (CSR), 46 °N–51 ° 30 ′N, 12 °E–25 °E (Strnad *et al.* 1976) Fig. 3.

The pattern of influenza A epidemics in the southern hemisphere is often very similar to that of those in the northern hemisphere, but the outbreaks south of the tropics are out of step with their northern counterparts by six months or less, as would be predicted if epidemicity were seasonally controlled. Figure 4 provides excellent examples (Gill and Murphy, 1976).

The influence of season upon the epidemic expression of type A influenza is therefore evident both in individual localities and upon a world scale. The seasonal influence, besides controlling the timing of epidemics, must also be somehow concerned in their unexplained termination in situations that favour their continuance by direct spread, in the disappearance and prolonged absences of the influenza A virus and in the reappearance of influenza, sometimes sudden, explosive and simultaneous over wide areas and vast populations.

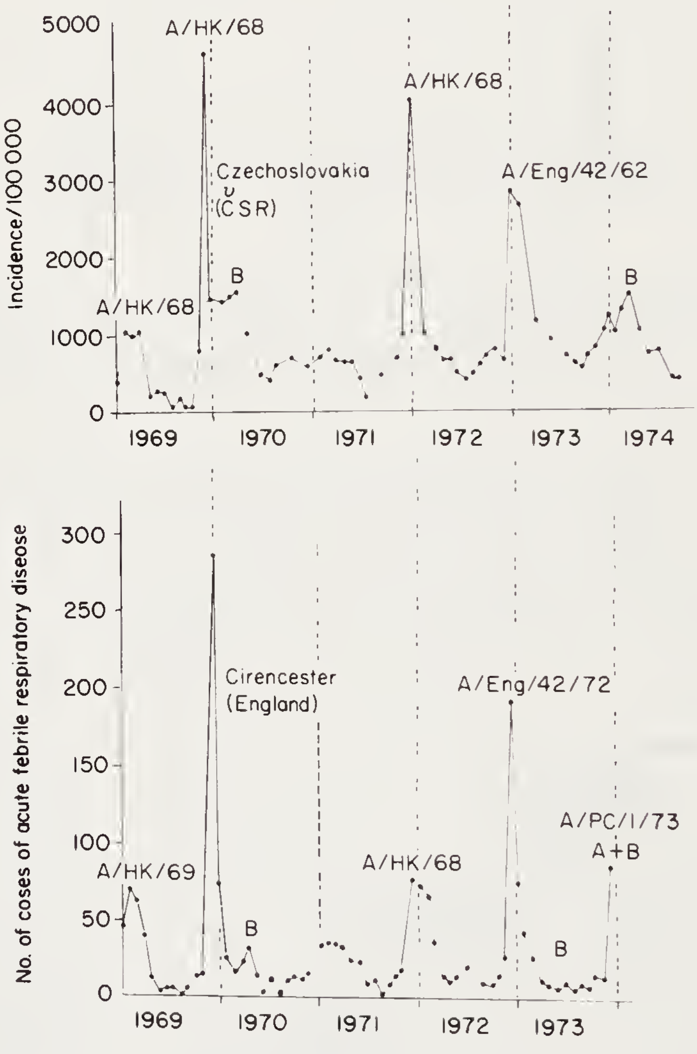

Fig. 3. Acute febrile respiratory diseases seen 1969–1973 in a general practice population in Cirencester, England, 53 °N 4 °W, compared with the incidence of acute respiratory diseases notified in Czechoslovakia (CSR, 46–52 ° 30 'N 12–25 °E), to show how epidemics caused by the same virus in populations living at about the same latitude may occur synchronously in widely separated longitudes. Similar synchronicity could have been shown with populations from northern America, e.g. Seattle, USA, 48 °N 124 °W (Foy *et al.*, 1976). CSR adapted from Strnad *et al.* (1976).

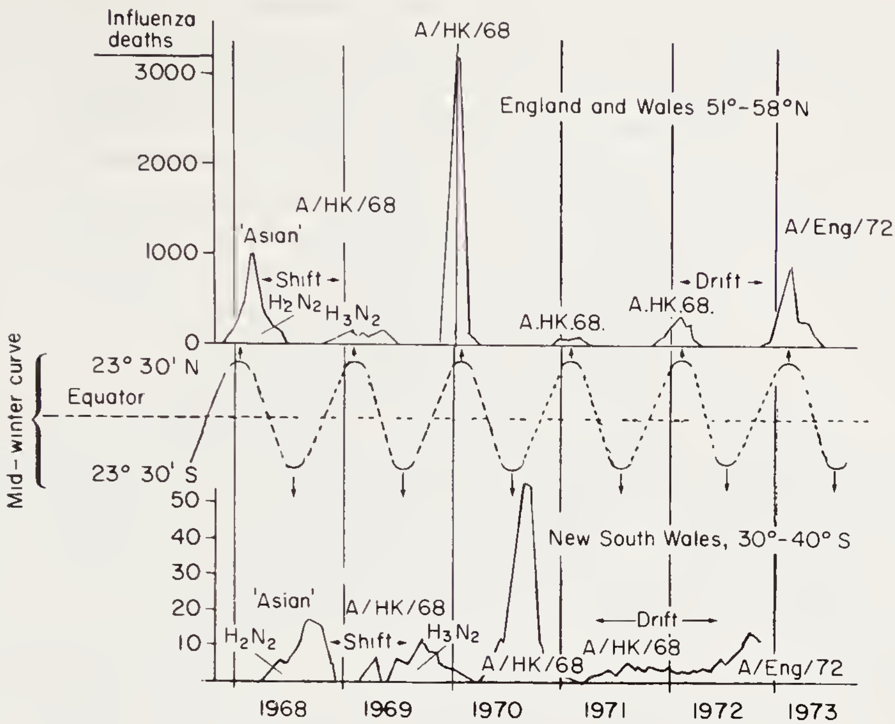

Fig. 4. Influenza mortality 1968–1973 in England and Wales, latitude 51–56 °N, compared with that in New South Wales, Australia, latitude 30–40 °S. Contrasting with Fig. 3 the effect of the widely separated latitudes is to produce a regular difference of about six months in the timing of the epidemic by the same virus in northern and southern hemispheres. The antigenic shift (1968–69) from H_2N_2 to H_3N_2 virus in UK precedes that in Australia. The drift (1971–72) appears to go from south to north but in fact one isolate of the new minor variant (A/Eng/42/72) was made in England six months before the Australian epidemic (Pereira *et al.*, 1977). (The Figure is adapted from Gill *et al.*, 1976.)

ANTIGENIC DRIFTS AND SHIFTS

Minor and major antigenic changes occur in influenza A virus, both of them important in relation to the seasonal epidemiology of the disease. Influenza immunizes its victim against further attack by viruses of the same major subtype because haemagglutinin (H) and neuraminidase (N), projecting as numerous spikes from the coat of the virus particles, are specifically antigenic. The antigenic changes in the virus therefore reflect changes in H or N or in both (Kilbourne, 1973; Monto and Kendal, 1973; Wrigley *et al.*, 1977).

Nature of antigenic drifts

Antigenic drifts are the minor changes in H, N, or both. They alter the virus distinguishably, but not sufficiently for the new minor variant readily to bypass the immunity left by influenza caused by other viruses of the same major subtype. Minor variants are classified by type of virus, location first isolated, laboratory number of prototype strain and year of isolation, e.g. A/Hong Kong/1/68 often shortened to A/HK/68, and A/England/42/72 often shortened to A/ENG/72.

The population of virus particles produced in an attack of influenza is not homogeneous. Particles representing the current epidemic strain are by far the most abundant, but a variety of minor mutants is always produced and drift occurs when a minor mutant replaces the current epidemic virus. The process of selection of a new variant is usually ascribed to *antibody pressure in a partially immunized community* or *herd immunity* (Delon *et al.* 1976; St. Groth and Hannoun, 1973) but reasons are given later in this paper for rejecting this assumption. Specific antibody is, however, the agent by which drift occurs. The natural process can be artificially reproduced by growing influenza A virus in cell culture or in animals in the presence of antibody (Archetti and Horsfall, 1950; Isaacs, 1951; St. Groth *et al.*, 1973). Yet influenza A virus induced to infect cell cultures persistently for long periods (Gavrilov *et al.*, 1972) has been found to undergo spontaneous antigenic drift identical with natural drift even in the absence of added antibody (Golubev *et al.*, 1975), so other factors besides antibody must also be involved.

Seasonality of antigenic drifts

Antigenic drifts occur frequently, often one or more annually, but a single minor variant may dominate the whole world for one or more influenza seasons. For example in mid-1975 A/Victoria/3/75 virus appeared at latitude 43°S in Australia and caused great epidemics in the southern hemisphere. In Great Britain (latitude 50–58°N) the three variants that had been concurrent all disappeared at the end of April 1975 and no influenza A virus was isolated until 31st December 1975 when A/Vic/3/75 appeared there for the first time and began to cause all the type A influenza in the UK and throughout the northern hemisphere (Pereira *et al.*, 1977).

Not uncommonly two or more minor variants co-exist in the same influenza season. They may be found in the same epidemic in the same small area, and two different minor variants have even been isolated on successive days, each from one of two small brothers sharing the same sick-bed.

An interepidemic interval of months or even a year or two when no influenza A virus can be found elapses between the influenza A epidemic seasons in any particular locality. When antigenic drift occurs the old minor variants that had been causing all the influenza usually disappear during the interepidemic interval and are entirely replaced next influenza season by the new minor variant. For example A/England/42/72 virus caused all the type A influenza in the UK in the influenza season of 1972–73 and was last isolated in Britain in mid-February 1973. The inter-epidemic virus-free interval lasted until October 1973, but A/Eng/72 did not then reappear. Instead a new minor variant, A/Port Chalmers/73, first found in New Zealand at latitude 45 °S appeared in the UK and caused all the type A influenza in Britain until June 1974 (Pereira *et al.*, 1977).

The unidentified seasonal influence is therefore involved in the seasonal changes of minor variants locally and in the sequential progress of drift from S. to N. latitudes and vice versa (Fig. 4).

Nature of antigenic shifts

Major changes of H and sometimes also of N, antigenic shifts, every ten years or so alter the virus sufficiently to enable the resulting major variant to bypass the immunity from attacks of influenza caused by its predecessor. A pandemic usually results in which the new variant surprisingly appears in many parts of the globe within twelve months and with its minor derivatives proceeds to dominate the world for a decade or so, usually causing all the type A influenza in the world until itself superseded by the next antigenic shift. Even more surprisingly each major variant has hitherto always disappeared from the world immediately before or at the time of the antigenic shift that produced its successor. For example *'Asian' influenza* A viruses were abundant in 1967 and in the first quarter of 1968 causing all the type A influenza in the world until May 1968, but, with the appearance of *'Hong Kong' influenza* viruses in July 1968, 'Asian' viruses were not again isolated anywhere in the world. Each new major variant with its derivative minor variants is accorded major subtype status and named by its H and N as follows: H_0N_1 viruses isolated before the pandemic of 1947, H_1N_1 viruses from 1947–1957, H_2N_2 viruses from the 'Asian' pandemic of 1957 until 1968, H_3N_2 viruses from the 'Hong Kong' pandemic of 1968 until the time of writing this paper, 17th August 1978. Viruses of H_1N_1 major subtype made an unexpected reappearance in 1977 after 20 years absence (PHLS, 1978) and are causing influenza concurrently with H_3N_2 viruses. The catastrophic influenza pandemic of 1918–19 was probably occasioned by shift from the then dominant unknown major subtype of influenza A virus to a new major variant considered to have been HSw_1N_1 virus which was probably in its turn supplanted at the pandemic of 1928–29 by H_0N_1 viruses (Langmuir and Schoenbaum, 1976). Another unexpected and alarming outbreak in the USA in 1976, fortunately small, was caused by HSw_1N_1 virus.

It might be expected that antigenic shift occurs because of the accumulation of progressive antigenic drifts, a major culmination of the minor processes. This view is widely believed to be mistaken, and the two processes are thought to differ in kind as well as in degree.

Shift can be produced by hybridizing influenza A virus parasites of different species of animals and birds and some of the hybrids have been shown to spread in epizootic fashion. Peptide analysis of H and N supports the suggestion that for example H_3N_2 virus may be a hybrid of human and animal viruses (Laver and Webster, 1973). The epidemiological difficulties of accepting fortuitous hybridization as the sole operative mechanism have led to hesitation in accepting the hypothesis.

Seasonality of antigenic shifts

When an antigenic shift occurs and the major subtype that had caused all the type A influenza in a particular locality for ten or eleven years disappears at the end of its last epidemic season, an interepidemic interval of months or years free of influenza A virus usually precedes the appearance of the new major subtype at the next influenza season. In Great Britain, for example, after H_0N_1 viruses had caused their last epidemic in 1945–46 season they disappeared and influenza A viruses were not again found until late in 1946 when H_1N_1 viruses began a big epidemic. Similarly, after the last UK epidemic caused by H_1N_1 viruses in the early months of 1956, the strain disappeared, and more than a year elapsed before H_2N_2 viruses were epidemic in the UK; first a few isolates in a military camp in June 1957, and then the awaited epidemic in September and October 1957. H_2N_2 viruses caused their last UK epidemic, a great one, in January–March 1968 and then they also disappeared. No influenza A viruses were isolated thereafter until December 1968 when H_3N_2 viruses made their first appearance.

The sequences just described were also taking place all over the surface of the globe, each in a single year or less, the actual timing of the change depending on the latitude. A good example can be seen in Fig. 4. There can be no doubt that season is somehow involved in the timing of whatever mechanisms produce antigenic shifts.

Sunspot cycles and antigenic shifts

Seasonality is a result of changes in the solar radiation received on earth. In a disease so influenced by season as type A influenza a coincidence with longer term cycles of variation in solar activity deserves to be mentioned (Hope-Simpson, 1976). Sunspot cycles from minimum to minimum of activity average 11 years, varying from 7–17 years. The true cycle is considered by solar scientists to be two consecutive 11 year cycles (Gibson, 1972). Each 11 year cycle consists of an increase of sunspot numbers to a maximum in about the 5th year followed by a slower decrease to a minimum in the 11th year. The solar radiation of the earth increases and decreases in parallel with the sunspot activity, and at sunspot maxima radio-magnetic activity reaching the earth is very much increased. The dates of known antigenic shifts, and of those presumed on reasonable evidence to have occurred, coincide closely with maxima of sunspot activity, so that *periods of dominance of successive major subtypes have synchronized with sunspot cycles* reckoned between sunspot maxima (Fig. 5). The association may be no more than a co-incidence. There is, however, as yet no explanation of the duration of the periods of subtype dominance and the solar-associated mechanisms underlying seasonality of type A influenza have yet to be elucidated.

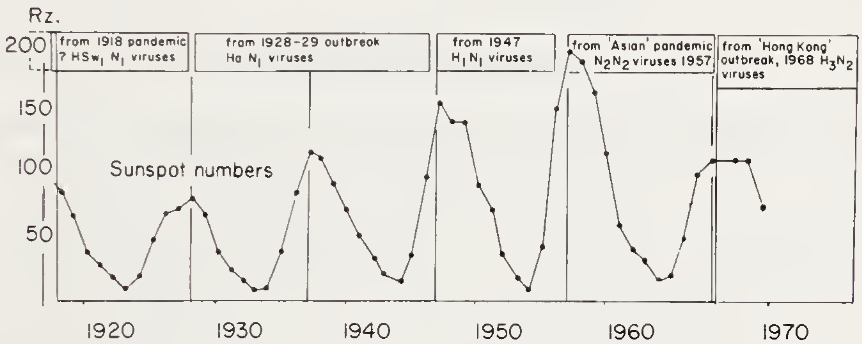

Fig. 5. Successive antigenic shifts of influenza A virus and subsequent periods of dominance of the resulting major subtypes compared with cycles of sunspot activity to show the correspondence. Each new major variant of influenza A virus appeared all over the world in less than nine months and disappeared abruptly during the interepidemic period after its last season of dominance before the next new variant appeared. Rz: Zurich yearly mean of daily relative sunspot numbers (From Hope-Simpson, 1978).

THE INFLUENCE OF SEASON AND LATITUDE ON RESPONSE TO LIVE INFLUENZA VACCINE

Further evidence on the importance of the unidentified seasonal influence was provided by observations in USSR on response to live influenza vaccine (Shadrin, Marinich and Toros, 1977). Two types of response were studied, firstly reactogenicity as shown by rises of body temperature and secondly antibody responses. These responses were examined at different times of year and at different latitudes with the following results:

Average percentage rise of body temperature in two north cities in European USSR, Murmansk 68 °N and Leningrad 60 °N:

Winter	6.7 %–8 %
Summer	0.8 %

Antibody responses showed a similar trend being 1.5 times higher after vaccination in winter than in summer in the towns of Leningrad 60 °N and Archangelsk 65 °N.

Average increases of body temperature in response to live vaccine given in autumn months in towns at different latitudes were:

Murmansk	68 °N	6.3–16.8 %
Krasnodev	40 °N	0.1 %

Seroconversions in different seasons in different latitudes were found as follows:

Murmansk	68 °N	May–Oct. 41.2–48.0 %.	Jan. 75.6–78.8 %
Krasnodev	40 °N	May–Oct. 5.7 %	Jan. 31.3 %

CONCLUSIONS

The influence of season and influenzal epidemiology

Seasonality is so closely integrated with type A influenza and the natural history of the virus that a seasonal influence must be at work in the mechanisms by which the virus multiplies and secures its continuity as a successful species. A hypothesis of the epidemiology of type A influenza that omits to take into account the influence of season must therefore be to some extent incorrect. The current hypothesis explains epidemic influenza solely by a mechanism of direct spread of the virus from influenza patients to their non-immune companions who promptly fall ill with influenza and so continue endless chains of transmissions. The progress of influenza across the African continent shown in Fig. 1 would usually be interpreted as illustrating such direct transmissions on a continental scale. Similarly the great sweep of a new variant of the virus, major or minor, every year or two, appearing in all parts of the globe within a twelve-month (Fig. 4) is usually interpreted as caused by direct spread, but the difficulties of accepting this simple explanation are insuperable. Not only is seasonality ignored, but also the long interepidemic intervals during which no virus can be found and no transmissions occur. No explanation is given of the cessation of epidemics in circumstances that favour direct spread, nor for the sudden reappearances of the disease often explosively over wide areas after months or years of absence of the virus. Burnet (1945) found himself compelled to the view that during the interepidemic period 'influenza virus must be harbouring in the tissues of human hosts in some form of latency'. Andrewes (1955) found 'evidence that influenza may be latent in a particular area to be activated when, with colder weather, things are more favourable for an epidemic. . . . We do not know where influenza lies concealed between epidemics . . .' He refers to 'the strange operative effect of season' as winter-factor, although he later draws attention to influenza epidemics in the tropics where the influence of season cannot be described as winter-factor. He and others (Dowdle *et al.*, 1974; Langmuir *et al.*, 1976) have sought to explain recurrences of epidemic influenza after long absences from an area by invoking an additional concept of 'seeding' of influenza virus, but the exact significance of the word is not made clear and probably varies with the author. However, it clearly indicates some kind of latent stage of the virus with presumably seasonal reactivations. Other authors, e.g. Marine *et al.*, 1976, faced with the same epidemiological conundrum, have simply remarked that the virus has 'remained in the area'. A coherent hypothesis of influenzal epidemiology is needed to give more precision to these and other concepts that must be invoked to explain the epidemic behaviour of the disease.

Suggested hypothesis of influenzal epidemiology

The following hypothesis, including both virus latency and a role for the unidentified influence of season, has recently been proposed:

(a) The influenza sufferer does not immediately transmit influenza virus to his non-immune companions because the virus rapidly becomes latent in his tissues and he becomes a carrier-host.
(b) The carrier-host has become specifically immunized by his attack of influenza. During the interepidemic months or years the latent virus causes him no disturbance and is inaccessible to present methods of discovery.
(c) When the next unidentified seasonal influence operates, the latent influenza virus residues are reactivated causing the carrier-host to become for a short time highly infectious to his non-immune companions while he himself suffers no illness.
(d) The reassembled progeny of the parent virus consists both of particles identical with the parent virions and of mutant particles of varied composition and abundance.
(e) Particles identical with the parent virion cannot escape from the carrier host because of his specific immunity.
(f) His non-immune companions are therefore presented with a small variety of minor mutants from which they unwittingly select the variant that is evolutionarily 'fittest' to procure the survival of influenza A virus species. These infected companions promptly develop influenza and themselves become the current epidemic before in their turn becoming carrier-hosts of latent virus whose reactivation next influenza season will precipitate among their non-immune companions yet another epidemic caused by yet another minor variant, and so on.

A few of many available examples have been given above of the world-wide operation of the seasonal influence in determining the timing of influenza A epidemics because, according to the hypothesis, it sets in motion reactivation of latent virus. The process leads inevitably to antigenic drift because after the interepidemic interval the antibody situation within the immune carrier-host must be similar to that obtained artificially in the laboratory experiments designed to procure antigenic drift of the virus. *Herd immunity* or *antibody pressure in the community* cannot cause antigenic drift because immune persons are spared in the process, and it is non-immune persons who develop influenza caused by the new minor variant. *Herd immunity* may more plausibly be invoked in the major process of antigenic shift, an evolutionary adaptation by which the influenza A virus escapes extinction when, after eleven years unchallenged dominion, the major sub-type is faced with an immunized population. At this critical moment it produces a major variant differing enough to be undeterred by the *herd immunity* it has caused. By contrast in the minor process of antigenic drift it is the non-immune persons who must be selecting, from the variety of mutants shed by their healthy companions in whom latent virus has been reactivated, the evolutionarily fittest minor variants best able by their abundance and spreading ability to secure the immediate future of the influenza A virus species.

The difficulties that were insoluble by the direct spread hypothesis disappear in the light of the presumed function of the seasonal influence. The virus that appeared to be absent for so many consecutive months or years was in reality lying latent all the time in carrier-hosts so there was no discontinuity. The epidemics that ceased unexpectedly when a high proportion of the community was non-immune and unattacked did so because the epidemic consisted entirely of the persons who had caught influenza from reactivated residues of the previous season's virus. At the time of their influenza they could not infect their non-immune companions, so the epidemic automatically stopped. Next influenza season, when their latent virus is reactivated, they will have their brief opportunity of infecting their companions.

The most baffling problem of all, that of the vanishing viruses, is simply solved. Variants that had uniquely dominated the whole world causing all the type A influenza for one or two influenza seasons have often disappeared during the interepidemic interval to be totally replaced everywhere next season by a new variant. The only way the mystery can be resolved is by the transformation of the old virus into the new variant as proposed in the new hypothesis.

Consequences of seasonal reactivation hypothesis

The latency-reactivation hypothesis, if it correctly interprets the epidemiological findings in type A influenza, carries important consequences. The disease has hitherto been looked upon as an infection spreading every year or two to all inhabited parts of the globe, travelling at unimaginable speed by direct transmissions from the sick to their susceptible companions. The picture presented by the new hypothesis is entirely different. It envisages that at any moment there are everywhere in the world numerous healthy carrier-hosts harbouring influenza A virus residues in a latent state. Every year – twice annually in the tropics – the unidentified seasonal influence travels north and south across the surface of the earth and, wherever it touches, it lights upon carrier-hosts summoning their latent virus residues to be reactivated into infectious virions and, if circumstances are propitious, to produce an epidemic. Some years have 'good' influenza seasons, some are 'bad' influenza years with no epidemic and little influenza. In some years the 'yield' of influenza varies in different parts of the world. The variability in the annual behaviour of epidemic type A influenza resembles that of many other seasonally controlled biological processes, and the causes of the variability are usually multiple and complex. Even in the leanest influenza seasons careful search in large populations will find a few cases of the disease.

What is the nature of the seasonal influence itself? It remains unidentified but we know a little better the sort of thing we are seeking. The search is for agencies that provoke reactivation of latent influenza A virus, and possibly also of latent forms of other *cold-season myxoviruses*, at times when solar radiation is most indirect and remote. The coincidence of successive major subtype dominances with sunspot cycles may be offering a clue to the action of the seasonal agency. Alternatively it may be indicating an association of influenza A virus with yet another solar process, or it may be a chance association, a phenomenon without any aetiological significance.

The evidence supporting the hypothesis of virus latency with seasonal reactivation automatically causing antigenic drift cannot be discussed here, nor the objections and the numerous exceptions when the process falls out of step in different parts of the world. The general picture is, however, clear and frequently repeated:

> 'The moving finger writes, and, having writ,
> Moves on . . .'

Many lives depend upon the correct interpretation of how and what the moving finger of season is year by year writing upon the population of the world using for ink type A influenza.

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Studies of Thermal and other Physical Environmental Influences on Oncogenic Viruses

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In Progress in Human Biometeorology, Part II, pp. 32–44 (Tromp, 1977) it was pointed out that statistically significant relationships have been observed between soil (Tromp, 1954; Tromp and Diehl, 1955; Griffith and Davies, 1954; Griffith, 1960; Stocks and Davies, 1960; Stocks, 1961) and climate (Krasnow, 1969) and the geographical distribution of cancer. These relationships could not be explained by geographical differences in nutritional or social factors. It has been suggested that the lack or abundance of certain trace elements (in particular Zn) in soil or drinking water, in certain areas, and in the food crops growing in those areas are responsible for the specific cancer distribution. However, it is often assumed that these statistically significant correlations are only apparent ones and that the true correlation must be sought in certain conditions in soil, water and climate which favours the development of oncogenic viruses.

In this connection Krasnow's observation (1969) is particularly important. He observed in 50 counties of the USA a highly significant negative correlation between temperature and malignancies of the large intestines and rectum, digestive system, stomach and breast. However, malignancies of the respiratory system showed a direct correlation with temperature. This observation strongly suggests that certain climatic (particularly thermal) conditions seem to stimulate the development of oncogenic processes and perhaps also the development of oncogenic viruses.

Several viruses are known which seem to be the causal agents of tumours in amphibia, birds and mammals. These tumour or oncogenic viruses include members of two main classes of viruses: those whose genetic material consists of deoxyribonucleic acid (DNA) and those containing ribonucleic acid (RNA). At least three DNA viruses are known to be oncogenic: the *adenoviruses*, the *papilloma* or *papova* viruses and the *polyoma* viruses. To the RNA oncogenic viruses belong those of the *avian leukosis complex* and the *mouse leukaemia viruses* (Williams, 1969). Many of the tumour viruses induce heritable, morphological changes in some normal cells infected in cultures, and this activity, known as transformation, seems to be a common property of all oncogenic viruses (Williams, 1969).

The first mammalian tumour to be identified with a DNA virus disease was the *rabbit papilloma* (Shope, 1933; Itoh, 1960). In 1911 Rous discovered that *chicken sarcoma* was caused by a RNA virus.

It is well known that many newborn animals, particularly rodents, are much more sensitive to oncogenic viruses than the adults (Huebner *et al.*, 1963). Hamsters are more responsive than rats or mice. This greater sensitivity of young animals is explained by the insufficiently developed antibody-producing mechanisms in young animals. The presence of actual or potential antibodies represents one of the principal means of an organism to combat the transformation of its cells into tumour cells.

In recent years it was also observed that amphibians are subject to the same range of neoplasms as found in higher vertebrates. Particularly the *Lucké* tumour, a renal adenocarcinoma of the leopard frog, *Rana pipiens*, is probably the best understood of the amphibian tumours. They are particularly common in leopard frogs from the North Central United States, but are extremely rare in N. Dakota and the Southern United States. These tumours seem to be caused by Herpes-like viruses and are transmitted through the frog embryos (Mulcare and Tweedell, 1967; Raffertry, 1963).

Significant *seasonal differences* were observed in the tumour prevalence (McKinnell, 1967). High incidence rates are reported from spring and autumn populations, whereas in summer the incidence is low. It is assumed that the presence or absence of virus particles in tumours detectable by electron microscope are climatologically determined (McKinnell, in Braun, 1969, p. 257).

The so-called '*winter*' *tumours* display cytopathic characteristics associated with the presence of a virus, whereas '*summer*' *tumours* lack virus. Thermal stimuli seem to determine whether a solid tumour contains or lacks *herpes virus* (Lambernard *et al.,* in Mizell, 1969). Low temperatures activate the production of herpes virus in summer tumours, which suggest that the complete viral *genome** is present in the 'virus free' tumour but only in a masked or latent state (Mizell, 1969). It is assumed that these seasonal oncogenic effects in amphibians are due to the influence of thermal stresses on the rate of immune response in amphibians (Evans, 1963; Evans *et al.*, 1965).

*The complete set of hereditary factors contained in the haploid set of chromosomes.

The influence of thermal stimuli on oncogenic processes was also demonstrated by the experiments of Fried (in Braun, 1969, p. 92).The temperature sensitive mutant of the polyoma virus Ts-a behaves like a normal virus at 31 °C. However, at 39 °C, the virus is unable to cause either a transformation or a productive infection (Frankel-Conrat, 1969).

Marek's disease, or *avian leukosis*, is another example of environmental effects on oncogenic processes. Marek's disease is a common infectious disease in domestic chicken in which there is both an inflammatory and neoplastic response of the lymphoid system. The tumour lesions often occur in the nervous system and visceral organs and seem to be caused by a herpes-type virus (Nazerian *et al.,* 1968). Atmospheric conditions which favour airborne transmission accelerate the transmission of the viruses and causation of the lymphoid tumours. At least four observations could support the theory that viruses, in particular herpes virus, may cause cancer in man (Roizman, in Braun, 1969, p. 478):

(i) Patients with severe and frequently recurring labial infections develop a squamous cell carcinoma (Wyburn-Mason, 1957).
(ii) There are at least two types of Herpes viruses, one of which causes an infection of the genitalia. On epidemiological grounds it has been assumed that cervix carcinoma in women is caused by this virus (Josey, Nahmias and Naib, 1968; Rawls *et al.*, 1968).
(iii) Herpes viruses cause important chromosomal breakages in non-permissive cells (Hamper and Ellison, 1961; Nichols, 1966).
(iv) The continuously observed association of herpes virus with different types of carcinoma, adenocarcinoma in frogs, in Marek's disease and in human lymphomas (Epstein, Achong and Barr, 1964).

In view of the great variety of herpes-type viruses in human cells many research workers assume that at least one and possibly all are inherently oncogenic (Roizman, 1969). Still many experts in this field do not believe in a viral causation of human cancer.

However, the various unexplainable, statistically significant, correlations which have been established between soil, water, climate and cancer (Tromp, 1954; Griffith *et al.*, 1954; Stocks and Davies, 1960), which cannot be explained with nutritional, trace elements, sociological and other medical-geographical factors, and the sensitivity of oncogenic viruses to thermal and other physical environmental factors strongly suggest that such a viral causation of human cancer and its geographical variation, at least in many instances, may be due to the different factors mentioned above.

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Studies on the Origin and Biological Effects of the Chinook in Western Canada

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INTRODUCTION

Although many studies have been made on the meteorological aspects of the *Chinook*, very little is known about the possible biological effects.

The *Chinook* is a warm, dry south westerly wind apparent during the winters in the Western USA (the states of Oregon and Washington) and in the Province of British Columbia in Western Canada. This warm wind comes from the direction of a district which was once inhabited by the Chinook Indians on the lower Columbia River (Rosen, 1979). The meteorological aspects of this wind resemble similar winds in Switzerland and Austria, known as *Foehn* (Von Deschwanden, in Tromp, 1977, pp. 142–147), the *Santa Anna* of S. California, the *Zonda* in Argentina etc.

In Switzerland the Foehn develops as humid air rises against the mountains in the Swiss Alps. This impact cools the air to such an extent that heavy precipitation occurs on the slopes of the Southern Alps. After crossing the mountains the air becomes dry and warm and reaches the valleys in the Northern Alps as a dry warm wind causing a number of important biological and clinical effects on the population living in these valleys.

In Canada the Chinook is known as the 'snow-eater'. It is a welcome wind during the Prairie winters. The west winds carry warm air from the Pacific over the mountains. As the air, rich in moisture from the oceans, condenses, heat is dissipated and the condensed moisture falls down on the Eastern Mountain slopes as snow. The warm dry wind, which crosses the mountains, passes the eastern prairies and cools by flowing over the very cold snow-covered ground. Although after a Chinook influx the wind is cooler after it reaches the Provinces of Saskatchewan and Manitoba, it is still relatively mild compared to the normal cold winds from the northwestern territories.

The warm dry Chinook, east of the Rocky Mountains, causes the snow to melt, the pasture is freed and starving animals can find some food again.

From the time of the early settlers in Canada, during the 19th century up to the present day, there is ample evidence to show that many farming and ranching communities in Southern Alberta during the winter depended on the arrival of the Chinook for their survival.

The change in temperature after a Chinook during a very cold winter can be considerable. A rise of 20 °C in less than 5 min is a normal phenomenon (Longley, 1972). According to Rosen (1978) the most spectacular Chinook in the annals of American meteorology occurred on 22 January 1943 at Rapid City in S Dakota (USA). The temperature rose in 2 min from −15 °C to +25 °C, 75 cm of snow disappeared in 12 h. This warm wind is called *Ta-Tekata* by the Sioux Indians.

METEOROLOGICAL CHARACTERISTICS OF THE CHINOOK

Glen (1975), Holmes and Hage (1971), Lester (1975, 1976a and b), Lester and MacPherson (1977), and Longley (1972) studied the meteorological mechanisms which are required for the development of a Chinook. They used aerial equipment during their observations in British Columbia.

Near the mountains the arrival of a Chinook is at times accompanied by a *Chinook Arch*. Altostratus clouds are formed in the warm air, which evaporate on reaching high mountain peaks. A bright band of sky appears below a dark grey cloud, a band which widens as the warm air moves eastward. The aerial studies have shown that the *Chinook Arch* cloud may extend up to 50 km in the wind direction and more than 900 km in the crosswind direction. It is embedded in the crest of a gravity wave of 95 km in length which persists for more than 10 h and moves Eastward at an average speed of 6 m/s. For further details see Holmes *et al.* (1971) and Lester *et al.* (1977).

BIOLOGICAL EFFECTS OF THE CHINOOK

Contrary to the Foehn, which has been studied in detail for its biological effects (see Von Deschwanden in Tromp, 1977, pp. 142–147), very little published information is available in the case of the Chinook. Whereas during Foehn weather many people experience unpleasant feelings (mainly as a result of serious thermoregulatory disturbances accompanied by hormonal shifts), during the very severe, cold, winters in Canada the Chinook gives respite from the severe cold stress and is experienced as a relief.

The Chinook has both beneficial and harmful effects. The rancher of S. Alberta depends on it to melt the snow so that the cattle can graze throughout the winter. Absence of the Chinook (e.g. in 1955–1956) is disastrous for the farmer. On the other hand removal of the snow by the strong warm dry wind decreases the moisture content of the soil required by spring crops. Particularly during the years when the Chinooks are numerous, the area becomes moisture deficient.

Although no systematic clinical studies have been made in relation to the Chinook the many observations made during Foehn weather or the *Chamsin* in Egypt and Israel enable us to predict the important changes which may occur in healthy subjects after a Chinook influx.

A sharp increase in environmental temperature usually causes the following physiological changes: contraction of the pupils, dilation of certain peripheral bloodvessels, reduced bloodpressure, reduced heart beat, reduced urinary output, reduced 17-ketosteroid urinary excretion but increased chloride and sodium excretion, increased blood coagulation time, reduced haemoglobin concentration, increased blood volume and bloodsedimentation rate, reduced capillary resistance, increased cellular permeability, reduction in antibodies, etc.

Hormonal studies by Sulman *et al.* (1970, 1975) suggest changed neurohormone secretion. Apart from changes in 17-ketosteroids also changes of 17-hydroxycorticosteroid levels in the blood, of adrenalin, noradrenalin, serotonin, histamin, thyroxin etc. have been observed.

Detailed studies in W. Canada of large healthy population groups before, during and after Chinook influxes, may confirm the existence of the above mentioned observations which could have a great effect on the general health, and the behaviour of large population groups.

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Industrial and Traffic Accidents

The Influence of Weather on Industrial Accidents

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PREVIOUS STUDIES

Several statistical studies were carried out on the possible relationship between weather and climate and the occurence of industrial accidents. Some of these reports are summarized in Medical Biometeorology (Tromp, 1977).

Important studies were made in Germany by Reiter (1952), Ungeheuer (1957), Richner (1974) and Dirnagl (1976).

Reiter (1970) observed a statistically significant relationship between an increased frequency of industrial accidents and certain important changes in weather conditions. Ungeheuer (1957) noted more frequent consultations of the industrial physicians shortly before, during and directly after a change of weather.

Daubert (1956), Mücher (1957), Apfelböck (1960), Mücher and Ungeheuer (1961) observed a significant correlation between advection of warm, usually subtropical airmasses and the rate of industrial accidents. Studies by Harlfinger and Jendritzky (1976) effectively confirm these results. On the other hand Akermann (1971) believes that there is only a weak correlation between these quantities while Cyran (1956) denied the very existence of any relationship. Wollkopf (1974) agrees with the results of Jendritzky and Reinke (1977) who used the same industrial accident data as Harlfinger *et al.* (1976) and Daubert's (1972) scheme of 'daily weather types'.

RECENT STUDIES

The statistical correlations with complex weather conditions proved to be a major difficulty in most of the previous biometeorological investigations. The present authors based their studies on the concepts of Brezowsky (1964) and Ungeheuer and Brezowsky (1965). They used the temperature-humidity environment (THE) parameter to describe the type of weather. The THE is calculated by comparing the actual water vapour pressure respectively to temperature, with the previous meteorological values of these parameters. The following formula is used:

$$\Delta X_i = X_i - \frac{\sum_{j=1}^{N} X_{i-j}(N-j+1)}{\sum_{j=1}^{N} j}$$

where: N = number of days of the previous period and X_i = the actual temperature or humidity parameter, measured at the first climatological date at 07.00 h.

This procedure has been applied to a time-series of data of industrial accidents which occurred in a great motor-car factory from 1974–1976 (Jendritzky, Rauschhofer and Sönning, in prep.).

The fluctuations of the daily numbers of accidents, with periods greater than one day, i.e. weekly, yearly etc. have been removed by numerical filtering (Jendritzky *et al.*, 1978, Jendritzky and Winkler, 1979).

The data collected in this way refer to the three categories of temperature (warmer–indifferent–cooler) and humidity respectively (less humid–indifferent–more humid). The results (Table 1), based on a previous period of N = 7 days, show only a weak relationship between the considered environmental parameters, although there is an observable trend.

Table 1. The frequency of industrial accidents in relation to temperature and humidity deviations

		N	$\bar{x}$	p (%)
ΔT(K)				
above	1.5	214	3.074	
±	1.5	296	2.998	4.0
below	1.5	198	2.969	
Δe(mbar)				
above	0.67	848	3.099	
±	0.67	202	2.963	1.8
below	0.67	258	2.892	
total		708	2.985	

where: N = number of days, $\bar{x}$ = frequency of industrial accidents /10 000 workers, p = level of significance (statistical parameter), ΔT (Δe) deviation of temperature (water vapour pressure) from the average of the past seven days.

The best correlations were obtained after combining the single parameters into the complex THE, which contains a considerable amount of information on the weather-conditions. It is remarkable that the degrec of statistical significance of the correlations between industrial accidents and weather depends mainly on the number, N, of the previous days.

Figure 1 shows the maximum of significance ($p = 0.02\,\%$) between $N = 14$ and $N = 21$ days. The significance level of 5% is already exceeded at the point of $N = 4$ and in the case of more lower values of N,

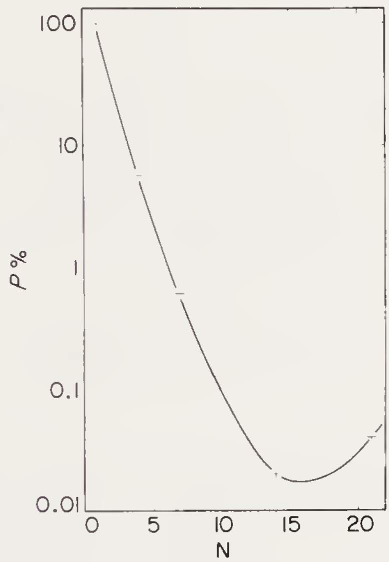

Fig. 1. Significance level, p, as a function of the number, N, of days included to specify the 'previous meteorological history'. The marks have been computed.

the differences in the frequencies of accidents are random. The results of computation with $N = 14$ days are given in Table 2.

Apparently an increasing frequency of industrial accidents is associated with a change into a more humid environment. The categories 1 and 4 (Table 2) indicate the increased biotropy at the front of a cyclone while category 7 is connected with the beginning advection of cold air masses. The categories 2, 3 and 9 which differ significantly from the above mentioned categories belong to the favourable anticyclonal weather conditions without the occurrence of biotropy. The category 5 of the THE, characterized by no change in respect to the previous meteorological conditions, is connected with a rate of industrial accidents close to the total average as expectcd.

It should be stressed that the THE – contrary to Dirnagl (1976) – has been interpreted only as an indicator of weather occurrenccs. It is difficult to assume a direct influence on the THE on the thermoregulatory system of man when considering the differences between

Table 2. Temperature-humidity environment (THE) and industrial accidents

NR	ΔT	Δe	N	$\bar{x}$	p %
1	a	a	169	3.122	
2	a	i	39	2.633	
3	a	b	11	2.745	
4	i	a	69	3.197	
5	i	i	114	2.933	0.02
6	i	b	77	3.049	
7	b	a	9	3.521	
8	b	i	20	2.960	
9	b	b	191	2.856	

where: NR = number of THE category, $\Delta T(\Delta e)$ = deviation of temperature (water vapour pressure) from the average of the past 14 days:

a = above the limit of 1.5 K (0.67 mbar)
b = below the limit of − 1.5 K (−0.67 mbar)
i = indifferent, $\Delta T(\Delta e)$ inside the limits

N = number of days
$\bar{x}$ = frequency of industrial accidents /10 000 workers
p = significance level

indoor and outdoor conditions (particularly in winter). Another problem is the observation that the THE given by the comparison of the actual environment, with the meteorological data of the previous $N = 14$ days give the best correlations with industrial accidents. It could be suggested that an adaptational process in humans may be involved. Furthermore it may be possible that strongly marked changes in weather are best filtered by this pattern.

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The Influence of Weather on Traffic Accidents

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INTRODUCTION

The direct influence of certain meteorological conditions on traffic accidents as a result of road conditions (snow, frost, wetness etc.) and poor visibility (due to snowfall, fog, heavy rain, air pollution etc.) is evident. Several studies were made of the possible indirect effect of weather and climate on traffic accidents. A summary of these physiological processes affected by changes in the weather is in 'Progress in Human Biometeorology' (Tromp, 1977).

Reiter (1952), King (1958, 1961), Möckel (1974), Sherretz and Farhar (1978) and others observed an increase in traffic accidents during rain or snowfall. Except for the latter two studies, the observations which were made suggest also an indirect meteorological effect on the physiology of the drivers.

Reiter (1952, 1960) observed a statistical relationship between a high incidence of traffic accidents, reduced reaction time and performance capability and pronounced variations of the atmospheric electric field. During days with strong disturbances of the normal spherics-activity an increase in accidents of up to 30% has been found.

Similar studies by Spann (1956), Spann and Ungeheuer (1956), Ungeheuer (1956), Köhn (1956, 1958) and Gohritz (1974) showed an increase of traffic accidents during biologically unfavourable weather conditions and a decrease during favourable days.

King (1958, 1961), Starzmann (1959), Horvath (1970), Runge and Malik (1970) and Maczynski (1972) tried to define into categories the direct and indirect influences of weather on traffic accidents. This is a difficult problem because both possible causes are often associated with the same weather situation. In order to analyse this problem a new investigation was carried out in the Saarbrücken-area (W. Germany) by Jendritzky *et al.* (1978).

METHODS

The input data of 18 302 traffic accidents and 1555 hit-and-run cases show the well-known weekly variations, with a minimum in the middle and maxima on Friday and Monday. This trend and all other long-periodic variations of these two time-series have been removed by numerical filters. The biosynoptical analysis of the weather situation has been made according to the *bioclimogram* of Becker and Ströder (1962). Additionally the observations and registrations of the principal climatological station Saarbrücken-St. Arnual have been used. During the study of the selected weather conditions simple correlation studies of averages have been carried out by using t-tests, multiple correlations by Duncan- or Scheffé-tests after a previous analysis of variance.

RESULTS

The correlations between the incidence of traffic accidents and weather parameters directly affecting accidents are shown in Table 1. This analysis covered 800 days of which 620 days showed a mean value of 17.2 traffic accidents/day, contrary to 15.4 for the remaining days. This indicates a difference of about 10 %.

The influence of fog, even thick fog, is statistically not significant (although there is a trend). Other meteorological parameters can cause an increase of accidents for example: from 10 %, during rain, to about 30 %, when icy-roads occur for the first time in winter. The computation of the latter data before filtering, i.e. the raw values, show a duplication in respect to the total mean value. Bad road conditions caused by any kind of precipitation (rain, snow etc.) is consequently an important factor of influence. In general, precipitation is a phenom-

Table 1. Relationship between various weather parameters and the incidence of traffic accidents

Weather parameter	No. of days	Deviation from expectancy in %	Significance level in %
Moderate fog visibility 200–1000 m	180	5.3	
Thick fog visibility <200 m	36	8.5	
Rain	360	10.0	0.1
Snow	105	13.6	0.1
Frost	105	12.0	1.0
Icy-roads (first time in winter)	5	28.6	5.0
Icy-roads	9	22.6	0.1

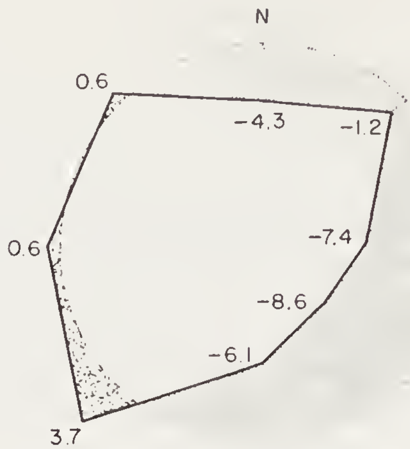

Fig. 1. Deviation of the incidence of traffic accidents (percentages) during anti-cyclone conditions arranged according to the point of the compass. (Saabrücken, 1969–1973)

enon of cyclonic weather conditions; widespread, persistent rain is caused by upslide movement of airflows and showers by turbulent vertical movement of air. Both processes are linked to biotropy irrespective of precipitation.

The weather conditions can be separated into two categories, *anti-cyclone* and *cyclone* conditions. Figures 1 and 2 show the relative

Fig. 2. Deviation of the incidence of traffic accidents (percentages) during cyclone conditions arranged according to the point of the compass. (Saarbrücken, 1969–1973)

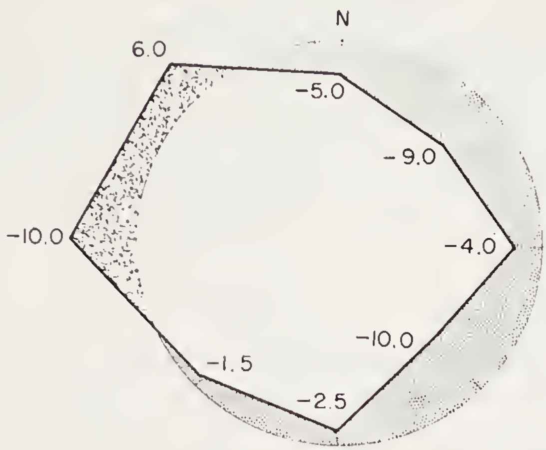

Fig. 3. Deviation of the probability of precipitation during cyclone conditions arranged according to the point of the compass. (Saarbrücken, 1969–1973)

incidence of traffic accidents. Except during south-westerly winds, anticyclone weather has a low probability of accidents. In Fig. 2 the meridional types of cyclone conditions are accentuated while there is only a small increase during westerly air flows and a distinct decrease during easterly air flows.

This may indicate that those weather conditions with a high probability of precipitation will lead to an increased incidence of traffic accidents; Fig. 3, however, shows little validity in this assumption. It is valid to say that the low probability of precipitation during easterly air flow is associated with a reduced number of traffic accidents; the increase in precipitation during westerly conditions can be correlated with an increase of traffic accidents. The considerable biotropic south and southwesterly winds, as well as the cyclone conditions with northerly air flow, show a high incidence of traffic accidents in spite of their low probability of precipitation. In the case of the trough situation the number of accidents is relatively low in spite of the characteristic heavy precipitation. In Table 2, therefore, all the atmospheric processes that are already regarded as biotropic have been associated with traffic accidents. The incidence of traffic accidents slightly deviates, but not significantly, from the total mean during subsiding airflows. Of course fog or frost may occur in connection with high-pressure situations and this may explain the unexpected positive deviation from the mean.

Upslide movement of an airflow, often accompanied by precipitation, causes only a small increase in the rate of traffic accidents, while the same process, without precipitation, shows a highly significant decrease. This may be due to the weak biotropy of west- or north-westerly weather conditions. However, the incidence of traffic

Table 2. The influence of selected weather types on the incidence of traffic accidents

Weather parameter	No. of days	Deviation from expectancy (%)	Significance level (%)
Subsidence of airflow (the whole day)	123	0.6	
Downslide movement	76	1.4	
Downslide movement preceding a weather change	31	1.6	
Upslide movement of airmasses	233	4.0	
Upslide movement of subtropical airmasses	83	9.2	1.0
Upslide movement of air without direct weather influences	70	−7.9	0.1
Upslide movement of subtropical airmasses without direct weather influences	35	11.5	1.0
Unstable weather processes	36	7.6	5.0

accidents increases during upslide movement of subtropical air masses to 11.5 % on days without precipitation.

The degree of intensity of biotropy has been classified according to different weather types. A highly significant increase of traffic accidents to 5.7 % can be observed during strongly biotropic conditions; during days without precipitation this value may even increase to 7 %, however, the difference between the two values may not be significant.

Although ordinary and hit-and-run traffic accidents are only weakly correlated (correlation coefficient $r = 0.3$), the cases of hit-and-run accidents coincide closely with strong biotropy. The incidence of hit-and-run accidents usually increases with icy roads, snow and frost. Turbulent vertical movements of air flows usually accompanied by an increase of traffic accidents (as a result of the high probability of precipitation) are negatively correlated with hit-and-run cases. One can therefore expect an increase of hit-and-run traffic accidents during those weather conditions affecting the reaction time and performance capability of car drivers.

CONCLUSIONS

It was found that apart from the direct effects of weather and climate on traffic accidents a car driver is also exposed to biotropic influences.

Traffic safety requires a harmonious combination of all the relevant psychosensoric and psychomotoric functions of the vegetative regulatory mechanisms (Luff, 1969; 1977). It would seem plausible therefore that the influence of meteorological stresses on the incidence of traffic accidents is of considerable significance. In order to reduce the number of traffic accidents it has been suggested to warn the public, through the media of radio, of weather conditions that may have strong meteorotropic effects. However, such proposed announcements may have a negative effect on psychologically unstable subjects leading to an unwanted increased incidence of traffic accidents.

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Month of Birth, Extra-terrestrial Influences, Time Series Analysis

Month of Birth and Mental Disorders

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INTRODUCTION

The possible relationship between month of birth and mental disorder has aroused more interest in the 1970s than during any earlier period of its short explorative history. A total of 147 800 cases of schizophrenia are included in the studies to be reviewed here, and 11 169 of those patients were born in the southern hemisphere. There can no longer be any reasonable doubt about the existence of a 'month-of-birth' effect in schizophrenia. More schizophrenic patients than expected seem to be born during winter and early spring months, although the cause of this phenomenon is still unknown.*

SCHIZOPHRENIA

Table 1 summarizes the findings of studies of schizophrenia published from 1973 up to late 1978.

Samples smaller than 1500 cases are not likely to yield significant results when deviations from expectancy are of the magnitude encountered here (5–10% by quarter of the year). Depending on the statistical method used, the critical sample size may be several times greater than this (Hare, 1975a; James, 1978). Negative results should be viewed against this background, especially since the question should not be as to whether seasonal deviations exist, but rather why they are not always found in adequate samples, and why they are greater in some subgroups than in others.

Koehler and Jacoby (1976a) suggested that diagnostic practices might explain negative findings similar to their own, which were based on a sample diagnosed strictly according to the criteria of Kurt Schneider. If this is true, it would mean that the seasonal phenomenon

* Two recent editorials discussed these findings and their implications (Editorial, 1978a; 1978b; see also discussion by Kellett, 1978; James, 1978; Moskovitz, 1978; Morgan, 1978; Torrey, 1978). A review of earlier literature in this and adjacent fields is found in Dalén (1975).
Editor's note: see also explanations given by Tromp (1963; 1977).

Table 1. Summary of studies of schizophrenia with ratio of observed to expected number of cases (O/E) during January to April (March), or other appropriate period in Southern Hemisphere studies

Author(s)	N	Country	Birth years	O/E		Comments
				January–April	January–March	
Danneel (1973)	698	West Germany		0.97	0.93	
Hare, Price and Slater (1974)	5139	England and Wales	1921–55		1.07	Preliminary report in Hare, Price and Slater (1973)
Ødegård (1974)	19 740	Norway	1870–1939			
Videbech, Weeke and Dupont (1974)	7427	Denmark	1901–55			
Woodruff, Guze and Clayton (1974)	22	Missouri, USA				
Dalén (1975)	17 592	Sweden	1901–40	1.06		Also in Dalén (1974)
	24 344	Sweden	1881–1950			
Diebold (1975)	730	West Germany		0.96	0.92	O/E for November–January = 1.18
Hare (1975b)	9760	England and Wales	1921–55		1.07	
Koehler and Jacoby (1976a)	1576	West Germany			1.05	
Krupinski, Stoller and King (1976)	3919	Australia	1910–59			No control data. Includes also a sample of patients born in the Northern Hemisphere
Larson and Nyman (1976)	406		1881–1918			
Parker and Neilson (1976)	2256	Australia	1905–59		1.05	O/E is for June–August O/E females (June–August) = 1.12
Parker and Balza (1977)	3508	The Philippines			1.15	O/E is for December–February O/E females (December–February) = 1.19
Shimura, Nakamura and Miura (1977)	2529	Japan	1841–1900	0.96	0.96	
	5431	Japan	1901–50	1.04	1.02	
Torrey, Torrey and Peterson (1977)	53 584	USA		1.05	1.04	
Hare (1978)	14 264	England and Wales	1921 60			
Parker (1978a)	1811	New Zealand			1.01	O/E for June–August
	236	Tasmania			1.14	O/E for June–August

belongs not to a 'nuclear' group of strictlv diagnosed cases of schizophrenia, but rather to some other subgroup of this heterogeneous disorder. This would agree with my own observations in data from Sweden and South Africa of a greater seasonal deviation in subgroups with a relatively good prognosis (Dalén, 1975).

Sex differences have only been found in two samples from the southern hemisphere, where the seasonal deviations were much greater in the female subgroups (S. Africa: Dalén, 1975; New South Wales: Parker and Neilson, 1976).

The seasonal pattern with excesses during winter and early spring months so far appears to be the same all over the world with a few exceptions. Dalén (1975) found a solitary June peak of births in a sample of patients from the northern part of Sweden, and Torrey, Torrey and Peterson (1977) found a June–July peak in three coastal South Atlantic states of the USA. A June excess is also seen in data from the whole of Sweden in birth years 1881–1900 (Dalén, 1975). Shimura, Nakamura and Miura (1977) found a marked excess of

Japanese schizophrenics born in May during the period 1841–1900. This may therefore be an older pattern or trend, which, for unknown reasons, is still extant in some parts of the world. Further evidence of a secular change was put forward by Hare (1978), who found a fourth-quarter excess in birth years 1921–30 in extensive data from England and Wales.

Ødegård (1974) subdivided his large Norwegian sample according to occupation at the time of first admission. He found seasonal deviations in all subgroups. This is important in view of current theories of social class and schizophrenia.

Pasamanick and Knobloch (1961) claimed to have found that significantly more schizophrenics were born following warm – compared with cool – summers in Ohio, USA. Their original data have not been published. McNeil *et al.* (1975) in Sweden, and Parker and Neilson (1976) in Australia failed to confirm this finding.

As originally suggested by Lang (1931) the season-of-birth phenomenon may simply be due to some peculiarity in the reproductive habits of the parents of schizophrenics, whereby there is an increase in the proportion of children born in these families during winter and early spring months. This can of course be tested by studying the month of birth of sibs of the patients. Hare (1976) found a first-quarter excess in a sample of sibs of schizophrenics combined with sibs of manic-depressive patients, this excess, however, can be accounted for by the existance of the sibs of manic-depressives alone. Larson and Nyman (1976) compared the month-of-birth distribution of 406 Swedish schizophrenic patients with that of their 1321 non-schizophrenic sibs. The two distributions were significantly different, and the sample of sibs does not show any significant deviation from appropriate population control data when January–April births are compared with those of the rest of the year. NcNeil, Kaij and Dzierzykray-Rogalska (1976) studied 315 sibs of Swedish schizophrenics; they showed a January–April excess that was only slightly smaller than that of the patients themselves. Buck and Simpson (1978) found no first-quarter excess among 1039 sibs of Canadian schizophrenics.

The evidence gathered so far does not favour Lang's hypothesis, and therefore the season-of-birth phenomenon is still likely to be directly, rather than indirectly, connected with the cause of the disease in a proportion of cases of schizophrenia. There is at present a dearth of potentially fruitful hypotheses in this field, and an unfortunate reluctance to follow the leads that have been published (for review see Dalén, 1975; Torrey *et al.*, 1977). This may be a consequence of the currently rather unimaginative theorizing on the causes of schizophrenia, which are widely believed to be either unitary, or vaguely multifactorial (Dalén, 1972).

Paranoia and schizophrenia are closely related, and there was a large and significant January–April excess in the sample of 2586 paranoia cases published by Dalén (1975).

MANIC - DEPRESSIVE PSYCHOSIS

There are few interesting findings of season-of-birth effects outside the diagnostic categories of schizophrenia and paranoia. Table 2 summarizes the results in manic-depressive psychosis. A first-quarter excess was found in data from England and Wales, especially in the subgroup of patients with mania. There is a weak parallel to these findings in Swedish and Australian data.

Table 2. Summary of studies of manic-depressive psychosis with ratio of observed to expected number of cases (O/E) during January to April (March), or other appropriate period in Southern Hemisphere studies

Author(s)	N	Country	Birth years	O/E		Comments
				January–April	January–March	
Hare, Price and Slater (1974)	3523	England and Wales	1921–55		1.09	Preliminary report in Hare, Price and Slater (1973)
Ødegård (1974)	6762	Norway	1870–1939			
Videbech, Weeke and Dupont (1974)	8212	Denmark	1901–50			
Dalén (1975)	15 646	Sweden	1901–50	1.01		Also in Dalén (1974)
Diebold (1975)	730	West Germany		1.01	0.98	
Hare (1975a)	7122	England and Wales	1921–55		1.05	
Koehler and Jacoby (1976b)	1215	West Germany			0.95	
Krupinski, Stoller and King (1976)	2202	Australia	1910–59			No control data. Also includes a sample of patients born in the Northern Hemisphere
Parker and Neilson (1976)	1317	Australia	1905–59		1.03	O/E is for June–August
Milstein *et al.* (1976)	56	Indiana, USA	1896–1952			
Hare (1978)	10 642	England and Wales	1921–60			
Hare, Price and Slater (1974)	533	England and Wales	1921–55		1.21	
Dalén (1975)	2267	Sweden	1901–50	1.03		
Hare (1975a)	1180	England and Wales	1921–55		1.13	
Koehler and Jacoby (1976b)	68	West Germany			0.96	
Parker and Neilson (1976)	220	Australia	1905–59		0.93	O/E is for June–August
Hare and Walter (1978)	1878	England and Wales	1921–55			

NEUROTIC DEPRESSION AND OTHER NEUROSES

Large samples of patients diagnosed neurotic depression have been studied by Hare, Price and Slater (1974), Dalén (1975), Hare (1975a), and Parker *et al.* (1976). The results are however entirely negative.

In the papers just mentioned, and in Hare (1975b), Koehler and Jacoby (1976a), Hare (1978), and Parker (1978b), there are also samples of patients with other neurotic disorders. The only notable finding is that of a 25% spring excess of Australian anxiety neurotics in the study of Parker and Neilson (1976), later confirmed in a new sample by Parker (1978b). These are the only studies where anxiety neurosis has been analysed separately.

PERSONALITY DISORDERS

Dalén (1975) found a significant 6% January–April excess of patients with a diagnosis of *persona pathologica* born in Sweden during the period 1911–40 (3540 cases). This finding has no parallel in large samples from England and Wales published by Hare *et al.* (1974), and Hare (1975a). The smaller samples of Diebold (1975), Koehler and Jacoby (1976a), and Parker *et al.* (1976) show a similar excess, though weak and non-significant.

OTHER DISORDERS

Kop (1977) studied the month-of-birth in relation to period of perpetration of 442 males convicted for aggressive offences, but the distribution by month of birth was unremarkable. The 592 suicide cases studied by Danneel (1975), as well as the 254 cases of suicide attempts of Beck and Lester (1973) showed no deviation by month of birth. This negative correlation also includes the samples of alcoholics studied by Dalén (1975), and Krupinski, Stoller and King (1976).

MENTAL RETARDATION

Jongbloet, Van Erkelens-Zwets and Holleman-van der Woude (1976) published a large sample of Dutch mental retardates – 20 135 cases including 2616 cases with Down's syndrome. The Down subgroup showed a January–April excess, which did not reach statistical significance. The other 17 519 cases showed a non-significant June–August excess (tests by present author, Chi-square with 1 d.f.). Small samples of mental retardation cases were published by Danneel (1973), Hare *et al.* (1973, 1974), Dalén (1975), and Parker and Neilson (1976). Their results were all negative. The earlier literature is quite extensive, but contains few significant findings (Dalén, 1975).* Mental retardation is known to be causally heterogeneous. This may also be the case with schizophrenia, manic-depressive psychosis, and other mental disorders. Anomalies in the distribution by month of birth may therefore be

*Janerich and Jacobson (1977a) proposed an endocrinological explanation of the bimodal seasonal excess (spring and autumn) of Down's syndrome found by Harlap (1974) in a series of only 103 cases. Their paper launched a discussion in the Lancet (Sever, 1977; Janerich and Jacobson, 1977b; Jongbloet and Van Erkelens-Zwets, 1977; Leck, 1977) connected with only one or a few of several different causes, all leading to more or less the same end state or disorder. Effects of season of birth in mental retardation should accordingly be sought in various subgroups of cases. There is no reason whatever to limit this search to conventional subgroups, new categories will evolve as research continues.

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Studies Suggesting Extra-terrestrial Influences (Apart from Solar Radiation) on Biological Phenomena and Physico-chemical Processes on Earth

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INTRODUCTION

Except for two short review papers by Tromp (1972a, 1975a) no up-to-date review has been published on recent observations suggesting extra-terrestrial influences (apart from the normal solar radiation effects) on biological phenomena and physico-chemical processes on earth. Many interesting papers preceding the period 1973–1978 were overlooked in the past and are now included in this paper.

At least eight different lines of research can be followed in the study of the possible effects of extra-terrestrial stimuli on the biosphere. The study of: (i) interdisciplinary cycle synchronies; (ii) changes of physical parameters in the atmosphere, of climatic changes and the outbreak of epidemics due to solar and planetary influences; (iii) cosmic ray effects; (iv) biomagnetic effects; (v) lunar and planetary effects on living organisms; (vi) worldwide changes in blood parameters of healthy population groups due to solar induced abnormal weather conditions; (vii) the Piccardi effect, and finally (viii) long-term (yearly) fluctuations (approximately 3–6 years) of erythrocyte sedimentation rates (ESR) in groups of healthy male blood donors in the bloodbanks of Leiden (The Netherlands), Århus (Denmark), Oslo (Norway), Lund (Sweden), Vienna (Austria) and Durban (S. Africa).

Each of these eight approaches strongly suggest the existence of unknown forces in our environment, either electromagnetic radiation, corpuscular radiation or gravitational waves, each of which has an extra-terrestrial origin. They could affect the biosphere either directly or indirectly. In the latter case the biological effects could be either due to the indirect result of direct effects on colloidal and other physico-chemical systems in the living organisms, or due to changes in weather and climate, which in turn may affect the entire organism.

A full discussion of each of the mentioned approaches and of all the references given at the end of this paper would require a monograph in itself. We shall therefore restrict ourselves to the principal observations of a large group of scientists studying the problem of possible extra-terrestrial influences on earth. The reader specifically interested in one of the above mentioned approaches can find the original sources in the list of references at the end of this paper.

INTERDISCIPLINARY CYCLE SYNCHRONIES

This approach seems to be the most difficult and least convincing approach, at least for a number of scientists.

According to Dewey (1971b), who introduced the concept of '*cycle synchrony*' cycle scientists have been fully aware of the fact that a cycle of a particular period, e.g. 5.9 years, is often also found in many other, apparently not related, phenomena. One could ask whether such cycle synchronies suggest a possible interrelationship between these phenomena. In any list of different cycles there will be some correspondence of period by chance alone. To determine the significance of such correspondence of period, it is necessary to take into account the total number of cycle periods, the degree of precision with which each period has been determined, the number of examples of each identity, and the number of identities.

A further difficulty arises in connection with the word *correspondence*. Measurements can never be exact. With cycles that are beclouded by randoms, even relatively exact measurement is difficult. We can merely assume that cycles which have approximately the same measurement of period may be different measurements of the same cycle. For example in a table one may group together all cycles measured as 5.89 years, 5.90 years, 5.91 years and 5.92 years and call them 5.9 year cycles. In this connection the question should be raised: To what degree of accuracy can a cycle be measured? This measurement depends on the regularity of the cycle and the number of times it appears in the relevant data.

A second striking observation in cycle analysis is that cycles of the same period tend to crest at or near the same point of time; e.g. in the case of the 18.2-year cycle, one could expect a crest at any time during the period if the cycles were caused endogenously. In fact one observes a pronounced '*clustering*' of the crest time; it therefore seems that this phenomenon is difficult to explain by chance only. It is even more surprising that this clustering phenomenon (cycle synchrony) is also observed in 6.0-year cycles, 9.6-year cycles etc.

Dewey (1971b) compiled in his paper 19 tables from 4-year cycles up to 54-year and 164-year cycles. Cycle synchronies were found in at least 38 examples of a 6-year cycle; 37 in 8-year cycles; 31 in 9.0-year cycles, and 35 in 54-year cycles etc. He concluded that cycles of the same period would not normally cluster unless they were related by cause and effect, or were the result of a common cause. It can therefore be argued in reverse that if cycles do synchronize in excess of what could be expected by chance there may be a relationship or a common cause that dictates such behaviour. At least, the behaviour cannot reasonably be random.

It should be noted that the synchrony will not be exact. Even if there is a known common cause it will not necessarily produce results that are timed with complete uniformity. The cycle of the day awakens birds, animals, and men at varying times. The cycle of spring arrives at various locations affecting the different species of plants at different times. The phenomenon observed is not complete synchronization of timing, but a clustering of turning points in excess of what is to be expected by chance.

A major problem in the study of cycle synchronies is to accept a common cause for entirely different, apparently non-related, phenomena. Since all the evidence points to worldwide environmental forces triggering the cycles, it has been suggested (Tromp, 1975b) that perhaps extra-terrestrial stimuli are involved as part of the observed cycle synchronies are astronomical cycles, e.g. sunspot cycles.

Support for worldwide-influences was given by Dewey (1971a) in his study of cyclic patterns in human aggression leading to national and international conflicts; the study of patterns in the mental processes of man and his behaviour. Dewey's study was based on the data collected by Wheeler (1951; 1960). Wheeler was formerly Chairman of the Department of Psychology at the University of Kansas. He prepared a year-by-year index of International War Battles for the period 600 BC–1943 AD and Civil War Battles of the period 600 BC–1941 AD. This index puts forward a parameter with which to measure the degree of aggression in the world at one time. The index was later extended by Shirk (1958) and Wheeler (1960) upto the year 1957. Time series analysis of this vast collection of material was carried out by Dewey and Vaux around 1968. Nine cycles were observed all of which, with one exception (53.5-year), were statistically highly significant ($0.006 > p > 0.0007$). The following cycle lengths were found: 6, 9.66, 11.25, 12.33, 17.75, 22, 53.5, 143 and 164 years. It could be shown that if random figures instead of Wheeler's data were used no cycles were found.

No theory of ultimate cause was proposed by Dewey for any of these cycles, but it seems most likely that the causes, whatever they are, are due to exogenous forces. The fact remains that international conflicts seem to have statistically highly significant cyclic patterns, even if the patterns have not been determined with absolute accuracy.

Editor's note: For references not included in the following reference list see Tromp (1972a; 1975a) where they are already cited.

If the index of human aggression has a pattern, and the statistical work of Dewey and Vaux shows indisputably that they do, all other considerations seem to be less important. A better index will, in the future, permit refinement of cycle length, cycle shape and cycle timing.

Recent studies by Alcock and Quittner (1978) of the Canadian Peace Research Institute established a number of statistically significant cycles, in connection with civil violence, until the year 2001. Three cycles (8.6-, 17.4- and 34-year) seem to predict changes in the global political system, while four cycles (5.6-, 9.4-, 20.5- and 54-year) predict changes in the global economic system. These changes in the political and economic systems could predict changes in the level of civil violence. Their studies were based on synchronic analyses of 58 nations and diachronic (across time) analyses of 24 nations over a period of 50 years. The results were statistically confirmed with extensive regression analyses. These studies also suggest worldwide environmental stimuli.

The many scientists working in the field of cycle synchronies seem to agree that these events are probably not caused primarily by terrestrial forces, but by extra-terrestrial triggers affecting also the mental processes in man in a similar way to the many wellknown biometeorological effects on mental processes (Tromp, 1972a). The physiological changes observed in 1974 in many parts of the world (Tromp, 1976a) seem to support this assumption.

CHANGES OF PHYSICAL PARAMETERS IN THE ATMOSPHERE, CLIMATIC CHANGES AND OUTBREAK OF EPIDEMICS DUE TO SOLAR AND PLANETARY INFLUENCES

A considerable amount of evidence is available which clearly demonstrates the effect of extra-terrestrial, in particular solar, forces on a number of physical parameters in the atmosphere:

(1) Solar eruptions affect the *UV radiation* of the atmosphere and the ozone content of the higher layers of the atmosphere; it changes the electric potential gradient in the lower troposphere, particularly after H-α solar flares, 1–3 days after the flare event; also the amount of radionuclides, such as Be^7 increases (Reiter, 1971, 1972, 1973, 1976) and geomagnetic storms (Roberts and Olson, 1973a) accompanied by Northern lights are observed. Considerable changes take place in the ionosphere which cause interference in transatlantic radio transmissions; these seem to be affected by planetary positions in relation to solar flares (Sanford, 1936; Huntington, 1948; Nelson, 1951; Bigg, 1967; Gribbin, 1973). This phenomenon enables us to give more precise predictions of transatlantic disturbances.

(2) According to Markson (1971), Bossolasco *et al.* (1972) and Herman and Goldberg (1978), solar events seem to influence the occurrence

and frequency of thunderstorms; also changes in *low pressure areas* at 10 000 m altitude a few days after solar eruptions have been observed (Schuurmans and Oort, 1969); King *et al.* (1977) described large standing planetary waves in the troposphere, causing changes in the atmospheric pressure in the troposphere; they seem to be caused by the 27.5 day solar rotation and the 11-year sunspot cycle; according to King (1973) the entry of solar wind particles into the atmosphere between 75 ° and 79 ° latitude may cause meteorological pressure changes; also the density and temperature of the atmosphere above 100 km vary markedly with solar activity. The exospheric temperature increases from *c.* 750 K at a sunspot minimum to *c.* 1200 K at sunspot maximum.

(3) Studies by Flohn (1951), London (1956), Markson (1971) and many others suggest *climatic changes* as a result of important solar events. Despite many recent studies on possible relationships between solar events and weather very little convincing evidence was put forward acceptable to most meteorologists. Studies by King (1973) suggest that in England abnormal winter and annual rainfalls occur during quiet solar conditions. The wettest and driest spring weather occurs mainly at times of very low or very high solar activity. The growing season in Scotland seems to be highly dependent on the sunspot cycle. Gribbin (1973) reviewed the studies by Winstanley, Lamb and others, suggesting a Southward shift of climatic zones after the previous 200-year period of Northward shift. This Southward shift could be responsible for the serious drought in the Sahel zone in Central Africa, south of the Sahara. It is estimated by Lamb that this shift of the Sahara in Africa and the Rajasthan desert in India would continue until the year 2030 due to a 200-year climatic cycle with a peak around 1930. It has also been suggested that the peak of 1930 actually marked the peak of a 700-year cycle, although this cycle has not been sufficiently established. It is most likely that these long term cycles are due to long term solar, planetary or other extra-terrestrial causes.

(4) Statistical evidence has also been collected on the influence of sunspots on the spreading of *volcanic dust* in the atmosphere and on long term temperature records (Mass and Schneider, 1977); studies by Tamrazyan (1972) have demonstrated that *mud volcanoes* in the USSR, common in oilfields, show a sharp increase in the number of eruptions when the *Apse line* of the lunar orbit is in the Syzygyzone.*

(5) Infectious epidemics on earth seem to be influenced by extra-terrestrial phenomena. Hope-Simpson (1979) observed in England that, in the case of influenza epidemics, dates of known antigenic shift in the population and dates of those presumed, on reasonable

***Apse line* is the imaginary line connecting the perigee and the apogee of the lunar orbit; *Syzygy* is the imaginary line passing through the earth, the moon and the sun.

evidence, to have occurred, coincide closely with maxima of sunspot activity; it can be concluded therefore that periods of dominance of successive major subtypes of influenza virus are synchronized with sunspot cycles between sunspot maxima.

Hoyle and Wickramasinghe (1977) suggested that cometary debris entering the earth's atmosphere may bring planetary viruses and bacteria which could cause epidemics in plants, animals and man. The primary comet dust infection would be the most lethal, whereas secondary, i.e. person to person, transmission would have a progressively reduced virulence.

Possible extra-terrestrial influences on polio and meningitis epidemics in Scandinavia have been suggested on the basis of highly significant statistical relationships between the maximum incidence of these epidemics and the Northern light phenomenon in Sweden (Hvistendahl, 1973).

COSMIC RAY EFFECTS

Observations made in Soviet and US space capsules since 1972, described extensively by Saunders (1973) and others, have shown *gravity* and *radiation effects* in the outer space both in animals and plants. In general little is known about *cosmic ray effects*. However recently a number of interesting experiments, published before 1973, came to our attention. These experiments were carried out near the surface of the earth but give a clue to possible cosmic ray effects at very high altitude.

Figge (1947), made some interesting experiments in 1946 on the influence of cosmic rays on cancer. 148 male mice were injected with 0.25 mg methylcholanthrene in sesam oil and developed carcinoma. The mice were equally distributed in 8 aluminium cages 11 × 11 × 4 in. Leadplates $\frac{1}{4}$ in thick were placed over 5 out of the 8 cages, about 3 in above the mice. When cosmic rays pass through thin sheets of metal they produce shower burst of ionizing radiations, which intensify the potency of the cosmic radiation. Figge found that mice exposed most to the effect of cosmic radiation developed the greatest number of tumours. After 10 weeks, of the 111 injected mice still alive after exposure to increased cosmic radiation, 84 developed carcinoma, whereas of the 67 mice, exposed to a lower level cosmic radiation, only 22 developed carcinoma.

Barnothy and Forro (1948) in Budapest studied the lethal effects of cosmic ray showers on the fertility of Angora rabbits and white mice by placing a lead cover of 16 mm thickness above the cages. Eugster and Hess (1955) in Switzerland kept test animals in cages covered with 18 mm of lead at 2340 mm altitude and studied changes in fertility. Their studies, however, were not conclusive.

Ong (1958, 1959, 1962, 1963, 1964a–d) in Peking studied, in a similar way, the influence of cosmic radiation on tuberculosis at high altitude and at sea level. Tuberculous mice exposed to reduced cosmic radiation at sea level, under 2 and 10 cm thick sheets of lead, showed significantly greater mean survival time than that of tuberculous mice exposed to direct cosmic radiation. Also the virulence and immunizing properties change at an altitude of 1897 m (i.e. stronger cosmic radiation), however, this may be due to other high altitude effects (e.g. reduced oxygen pressure) (Tromp, 1963).

Planel *et al.* (1970a) studied the growth of cultures of *Paramecium caudatum* and *Paramecium aurelia* in the underground laboratory in Moulis (Arîège), which belongs to the Centre National de Recherches Scientifique in France. The cultures subjected to strongly reduced cosmic radiation showed a delay in development and a lengthening of the cellular cycle. These studies confirmed previous findings of the same authors using 5–10 cm thick lead plates above the cultures in an overground laboratory.

Similar results were found by Planel *et al.* (1967), using *Drosophila melanogaster*. Planel *et al.* (1971) also studied the effect of reduced cosmic and other ionizing radiation on the growth of human cancer cells of the type KB and HEP-2. Lead plates of 5 cm thickness reduced the growth rate by 8%; under 10 cm plates the reduction was 14%.

Rothen (1975a and b) observed a 24-h periodicity in the antigen activity of nickel coated glass slides used for carrying out immunological reactions at a liquid/solid interface. The $12 \times 0.5 \times 0.15$ cm glass slides are coated with a nickel layer ($\simeq 4000$ Å thick) by evaporation in vacuum. The coated slide is immersed in a solution containing 10^{-3} g/ml of antigen, either a protein or polysaccharide. As a result a 30–40 Å thick monomolecular layer of antigen is absorbed onto the slide. The layer is inactivated by solar radiation but recovers its activity at sunset and remains active till the next sunrise. However, the reactivation at night can be stopped if the slide is surrounded by 3.5 cm of lead. These and other observations of Rothen lead him to believe that the reactions are strongly influenced by soft cosmic radiations which are stopped by a 3.5 cm lead cover.

Waddington (1972) studied the variations in intensity and chemical composition of cosmic radiation during a solar cycle. It can be simulated by assuming a heliocentric decelerating potential that is applied to the particles arriving from interstellar space. The actual mechanisms involved in the reported biological effects are still unknown.

BIOMAGNETIC EFFECTS

The existence of biological effects of extra-terrestrial magnetic fields is supported by the findings of Brown and Park (1965) that planarians react to extremely weak magnetic and electromagnetic fields similar in strength to the magnetic disturbances observed during solar flares.

Reid *et al.* (1976) correlated extinctions of faunal species with coincidental reversals in polarity of the geomagnetic field due to depletions of stratospheric ozone, which is caused by solar-proton irradiation over a reduced geomagnetic field.

Further data on biological effects of weak magnetic fields were compiled by Barnothy in *Progress in Human Biometeorology* (ed. S.W. Tromp) Part IA 1977, pp. 392–399.

LUNAR AND PLANETARY EFFECTS ON LIVING ORGANISMS

A number of studies have been reported on the tidal effects of the moon. Recently Quartier (1970) described in a 10-year study (1959–1968) the indirect effect of the moon on the amount of trout caught in Lake Neuchâtel in Switzerland. A careful analysis of the data by the Physical Institute of the University of Neuchâtel has shown a minimum during full moon and a maximum just before or just after new moon.

Nouvel (1945) of the Oceanographic Institute of Monaco, and Wheeler (1937) in the USA, described lunar effects on crustaceans (e.g. *Anchistioides*). Renewal of the shells, sexual activities and regeneration phenomena show clear relationships with lunar tidal movements. Naylor, Atkinson and Williams (1971) reported on tidal rhythms in locomotor activity of the shore crab *Carcinus maemas L.* When their eye stalks were removed neither did they show a tidal rhythm, nor could they be induced to show a rhythm after chilling, (a stimulus that normally induces a tidal rhythm in crabs).

Marguerite Webb (1965, 1971), Brown *et al.* (1953), Barnwell (1966) and others described tidal rhythms in the locomotor activity of the Fiddler crab, *Uca pugnax*. Palmer (1967) observed similar phenomena in the crab species *Sesarma*.

Caspers (1951) observed, in *Clunio marinus*, a rhythmicity in reproduction related to the various quarters of the moon.

Several interesting studies have been made on the Palolo worm, *Eunice viridis*, which lives on the coral islands of the South Pacific, particularly near Samoa and the Fiji Islands. During the reproductive period the terminal part of their bodies fall off and spread over the surface of the water where fertilization takes place. This event occurs in October and November, but only during the last quarter of the moon. In the Atlantic Ocean a similar worm species reproduces in June or July during the first quarter of the moon.

In these various instances both lunar light and gravity effects, and perhaps temperature effects as a result of the tidal movements, seem to play a role in the reproductive activity of these worms and it is difficult to decide which of these factors has a dominating influence. Studies by Korringa (1947), a biologist of The Netherlands Institute for Fishery Research, have shown that at least in oysters (*Ostrea edulis*) living in the Easter Schelde (SW Netherlands), gravity seems to be the most important factor. Periods of maximum and minimum egg production of the oyster population are not related to the temperature of the water or light intensity of the moon. The maximum occurs ten days after new and full moon, particularly during the spring-tide.

Lang and co-workers (1977), of the Zoological Institute at Göttingen, Germany, demonstrated that the guppy-fish (*Lebistes reticulatus*) has a lunar periodicity of colour sense on the dorsal side. In yellow light (583 nm) the sensitivity values are smaller at new moon and greatest at full moon; in violet light (432 nm) the inverse applies. At the first quarter there is a secondary minimum and respective maximum. A statistical t-test gave $p < 10^{-7}$. As the fish lives under conditions of constant light and gravity the actual cause of the phenomenon is still unexplained. It is possible that the fish reacts to lunar induced micro-seismic activity of the earth as demonstrated for the eel by Deelder in Den Helder (N. Holland).

Dresler (1940) established a lunar periodicity in the colour sense of man for green (546 nm) and orange (589 nm) light. Maximum values for the quotients of the two sensitivities were observed during full moon. Dresler's findings were confirmed by Kohlrausch (1943).

Still Campbell and Beets (1978) of the University of Kansas, in an extensive review of reported possible relationships between phases of the moon and human behaviour (as shown in psychiatric hospital admissions, suicides, homicides etc.), concluded that lunar phase is not related to human behaviour. In this connection it is worthwhile to mention the findings of Kardas (1976), formerly attached to the University of La Laguna, Tenerife (Canary Islands) who observed statistically significant differences in certain forms of human behaviour (e.g. driving accidents and crimes) on days of high and low solar activity. Drivers make less mistakes while on the road ($p = 0.05$) on days of low solar activity, whereas more crimes are committed on these days.

Klinowska (1972) demonstrated lunar rhythms in activity, urinary volume and acidity in the golden hamster. Urinary volume showed a maximum, and activity a minimum, on the same day of the lunar month. While the pH showed a minimum on almost the same day as the peak in activity and a maximum at about full moon.

Oehmke (1973) described lunar periodicity in flight activity of honey bees in Morocco under field conditions and in a rearing room in Frankfurt. As temperature, humidity, light intensity and food supply were kept constant during the experimentation, these factors cannot be the only exogenous 'Zeitgebers'.* He assumed that a lunar induced periodical change in gravity on earth could be partly responsible for his observation.

Stutz (1973) described a synodic monthly rhythm of spontaneous

*Internationally accepted term introduced by Aschoff for the most dominant external factor determining a rhythmic process, e.g. light, temperature.

activity in the Mongolian gerbil. Minima occur around the last quarter and several days before full moon. This pattern persists for the summer, fall and spring cycles. The winter cycle is a mirror image of the former three. There is a similarity in cycle form among the gerbil, hamster (Klinowska, 1970), mealworm (Campbell, 1964) and planarians (Brown and Park, 1965). This similarity and the phase synchronization suggests, according to Stutz, that all organisms seem to be affected by an unknown environmental factor(s).

Empirical studies by F. and M. Gauquelin (1971, 1972) suggest statistically significant relationships between certain planetary positions, daily cycle of birth, the time of birth of 'successful professionals', heredity and other similar phenomena. Further studies will be required to confirm the significance of these statistical correlations which are difficult to understand with our present knowledge.

Similar effects of the moon on the behaviour of plants have been reported. Only three examples will be discussed here. Burr (1945), former professor of neuro-anatomy at Yale University in the USA, studied the daily fluctuations in electric potentials of growing trees by placing two electrodes 1.5 m apart in the cambium of trees. The observed fluctuations do not show any significant relationship either with atmospheric pressure, temperature or humidity of the atmosphere. Studies by Burr and Ravitz (1946) suggest that lunar tidal effects on the plant saps in the trees may be responsible for these rhythmic fluctuations. They could show similar fluctuations in the skin potentials of human subjects which reached a maximum during full and new moon. However, it is possible that it is not the tidal but photoperiodical effects which are involved in these fluctuating tree potentials.

In California Dunlap (1951 – verbal information) reported on the South African Iris variety *Morea iridoides* which flowers twice a month. The first flowering begins on the first day of the 1st quarter and finishes a day before full moon. No flowering occurs during new and full moon.

Finally Best (1978) summarized the work of a large number of botanists and concluded that two different lunar cycles apparently seem to affect plantgrowth.

Apart from lunar effects Gribbin (1973) suggested that planetary alignment and solar activity may effect climatic change and thus have an indirect effect on the biosphere.

WORLDWIDE CHANGES IN BLOODPARAMETERS OF HEALTHY POPULATION GROUPS DUE TO SOLAR INDUCED ABNORMAL WEATHER CONDITIONS

During the year 1974 world wide meteorological conditions were most abnormal. Continuous recordings by Tromp of a series of bloodparameters (since 1955), made at the bloodbanks of Leiden (The

Netherlands), Oslo (Norway) and Durban (S Africa), enabled Tromp (1976) to compare sudden changes of different bloodparameters of large healthy male population groups with the abnormal meteorological events. Statistically significant changes were observed in the erythrocyte sedimentation rate, the haemoglobin, albumin, γ-globulin and bloodpressure patterns of these large blooddonor groups.

THE PICCARDI EFFECT

Around 1935 Piccardi (Piccardi, 1962), professor of physical chemistry in Florence, started long range studies on the still unknown causes of certain non-reproduceable physico-chemical processes in water. In 1938 he had already assumed they were related to unknown external physical phenomena. Many chemical systems were tested upto 1950, all of them heterogeneous systems in evolution such as: (i) precipitation of bismuth oxychloride from bismuth chloride by hydrolysis using distilled water, (ii) precipitation of colloidal arsenic trisulphite of a silverhalide, (iii) of calcium sulphate to name but a few. Piccardi realized that these heterogeneous systems (which have not reached equilibrium) such as colloidal systems, are sensitive indicators of the changing external physical environment.

In February 1951 he started with a daily series of so-called *differential tests*, based on his previous observation in 1936 that a metal screen (not a cardboard screen) is sometimes capable of modifying a chemical process such as the degree of activation of water, the activation being the result of an electric charge created by a drop of mercury in a glass globe filled with neon gas. Bismuth chloride was used in his experiments, which precipitates with an addition of distilled water as bismuth oxychloride after hydrolysis. Piccardi compared the rate of precipitation of bismuth oxychloride in 10 small plastic cups covered by a metal screen (e.g. copper) for a duration of 2 min, with that of 10 uncovered cups. A number of precautionary measures had to be taken to standardize this method and to exclude mechanical errors. Capel-Boute (1955; 1962) lecturer in electro-chemistry at the University of Brussels, was largely responsible for these technical improvements of the procedures. Since 1955 the Piccardi test has also been carried out daily in Brussels. Similar experiments were carried out by the physician Giordano in Italy (1957), by Itoh, Tsugioka and Saito (1959) in Japan, in the Antarctic (Verfaillie, 1969), Austria (Fritsch, 1954, 1955), Lake Como (Solimene and Gualtierotti, 1972, unpublished report) in the Belgian Congo (by a member of the meteorological service; verbal information) and at Kerguelen Island (lat. 80 °S). Since September 1969 systematic experiments were carried out in the Biometeorological Research Centre, Leiden, The Netherlands (Tromp, 1975).

Some of the major findings of these long series of daily tests are the following:

(1) The changes observed in a daily basis, or monthly average, are not related to environmental temperature changes, windspeed, humidity etc. It is only the rapidity of the whole test which is accelerated with rising temperature in both groups of 10 cups.

(2) Studies in Tübingen at the Astronomical Observatory (Siedentopf, 1958) suggest slight differences in precipitation between groups during day and night.

(3) Experiments in 1954 carried out in Austria by Fritsch (1954, 1955), of the Vienna Technical University, together with Piccardi at the mountains of Kaprun Mooserboden (2000 m), Kaprun Werksiedlung (800 m), Tübingen, Germany (328 m) by Siedentopf (1958), and at Jungfraujoch, Switzerland (3578 m), suggest lower values for the so-called *p*-tests at higher altitudes.

(4) Capel-Boute (1962) observed certain latitude effects.

(5) Becker (1955), of the Fraunhofer Institut at Freiburg, using 5 day averages found a statistically highly significant correlation between the Piccardi precipitation curves and the curve of the daily relative sunspot number. Certain types of tests seem to correlate better with solar eruptions and magnetic storms. The relationship was lacking in cups completely covered with a copper screen.

(6) Experiments by Eichmeier and Büger (1969) and Baumer and Eichmeier (1978) in the Institute for Technical Electronics in Munich (Germany) showed the effect of electromagnetic radiation on the rate of precipitation of colloids; precipitation was accelerated under infrared radiation, or under copper or lead screens, and decelerated under UV-, X- or γ-radiation. Visible light had no clear effect.

(7) Studies by Fischer *et al.* (1968) in the laboratory of Atmospheric Sciences at Boulder, Colorado, using silica colloidal systems, showed that alternating electromagnetic and non-static electrical fields applied to colloidal systems or to their suspending media, result in increases in precipitation rate, electrophoretic mobility, resistivity, and viscosity. On the other hand magnetic fields and static electric fields result in decreasing precipitation rates.

(8) Tromp's experiments (1975), using the *p*-test only (copper screen), confirmed the findings of Piccardi, Capel-Boute and others. None of the present known meteorological factors seem to be able to explain these fluctuations in precipitation speed.

Verfaillie (1969) made extensive studies at Euratom-Ital in Wageningen, The Netherlands, of the effect of environmental physical factors on the growth rate of *Ballila* rice seedlings at Ispra. He noted that the mean values did not vary at random but fluctuated with time, like the intensity of many geophysical phenomena. This made him study possible correlations between the rate of growth and the intensity fluctuation of cosmic rays, geomagnetic activity and the P-indices of

Piccardi. A careful statistical analysis (Verfaillie, 1969) revealed a strong negative correlation between the P-indices and growthrate, and between the P-indices and the coefficient of variation. Verfaillie assumes that these biological effects are due to electromagnetic radiations accompanying solar eruptions, whereas the chemical test seems to be influenced by the subsequent corpuscular emission of the sun. This could be explained by the fact that solar emissions accompanying a solar eruption, are of two kinds, electromagnetic and corpuscular. Studies of geomagnetic storms (Chapman and Bartels, 1940) have shown that the electromagnetic waves travel at the speed of light and reach the earth in about 8 min giving rise to the short Sun Flare Effect which comes 21 h before the beginning of the geomagnetic storm. On the other hand 21 h after the beginning of the eruption, a corpuscular front travelling at a speed of 2000 km/s reaches the earth, giving rise to ionospheric effects that can last for a few days. Similar biological studies in relation to the Piccardi test were carried out by Abrami and Piccardi (1972). Fluctuations in seed germination of *Chenopodium botrys*, under strictly controlled environmental conditions of temperature, humidity and barometric pressure, showed significant correlations with the P-test of Piccardi.

Experiments by Piccardi in 1956 have shown that the bloodclotting time of human blood, recorded inside a box of thin (1 mm thick) copper sheeting, is usually longer than outside the box. In other years a contradictory result was observed. Itoh *et al.* (1959) repeated his experiments with rabbit blood, using the method of Sahlil and Fonio. He found that if the percentage ratio of inside/outside values was low, during the P-test of Piccardi, then the clotting time was low and vice versa. The results of this biological P-test of Itoh were statistically highly significant.

All scientists studying the Piccardi phenomenon agree that the phenomena observed are due to changes in the structure of the water used in the experiments. Many physicochemical studies in recent years, using conductivity or viscosity measurements, have shown beyond doubt that water is not such a simple constant substance as usually believed, but a fluid highly sensitive to physical environmental stimuli. In view of the various observations briefly summarized above it is very likely that the physico-chemical changes in the water are related to unknown extraterrestrial radiation stimuli.

The existence of unknown radiation phenomena in our environment is supported by the observation that the erythrocyte sedimentation rates depend on the location of the experimental site on the earths surface, the elevation in buildings and whether metal screens are present or not above the precipitation test tubes (Tromp and Van Veen 1976). Further research is recommended in order to study the reported changes in capillary patterns in experiments using clotting paper hanging in metal solutions during planetary conjunctions, under constant environmental temperature and humidity conditions (Kolisko, 1927; 1928; Schwenk, 1949; Kollerstrom and Drummond, 1976).

LONG TERM (YEARLY) FLUCTUATIONS (APPROXIMATELY 3–6 YEARS) OF ERYTHROCYTE SEDIMENTATION RATES (ESR) IN GROUPS OF HEALTHY MALE BLOOD DONORS

These phenomena have been studied by Tromp, particularly at Leiden since 1955, in Århus since 1968, in Oslo since 1963, in Lund since 1971, in Vienna since 1968 and Durban. S Africa since 1969, and in fifteen other bloodbanks in the Northern and Southern hemispheres. Particularly the studies carried out at the Biometeorological Research Centre, Leiden, on the physico-chemical state of the blood of healthy male blood donors (a total number of 11 200/year) have revealed that most likely worldwide acting environmental forces affect both inorganic (Piccardi phenomenon), and organic colloids (human erythrocyte sedimentation rate). An ever increasing amount of evidence is accumulating that these forces are actually extraterrestrial of unknown origin, most likely of an electromagnetic nature.

Of the 18 analysed bloodparameters particularly interesting results were obtained with *erythrocyte sedimentation rate* (ESR) (Tromp, 1967c), *haemoglobin* (Hb) (Tromp, 1967a), *serum albumin* and *γ-globulin* (Tromp, 1967b) and *diastolic bloodpressure* (Tromp, 1969). A frequency distribution analysis of thousands of ESR values observed at Leiden showed that the ESR value of 2 mm/1st hr (determined with the Westergren method) is by far the most frequently observed value, followed by 1 mm values. The total number of 1 and 2 mm values observed during each donor day usually exceeds, by more than 100 %, the 3–4 mm and higher ESR values. For this reason the percentage of male donors per donor day (i.e. a day during which 100–200 donors visit the bloodbank at Leiden), with ESR values of 1–2 mm/1st hr, were used as an ESR parameter for each donor day. These percentages may exceed 70 % on certain days, whereas values below 20 % may occur on other days. Fibrinogen studies with more than 790 male donors have shown that the ESR fluctuations are mainly due to fluctuations in the fibrinogen content of human blood produced by the liver.

A detailed analysis of the ESR percentages has shown that both short-term (daily or weekly) and long-term changes in ESR pattern occur. The latter are either monthly changes (seasonal or pseudo-seasonal) or very long-term yearly fluctuations. All these fluctuations except the yearly changes are sharply inversely correlated with the average *cooling index* (the combined effect of temperature and wind). However, the yearly fluctuations cannot be correlated with any changes in meteorological, sociological or food factors. The data suggest the existence of both 3-year and 6-year cycles. Since 1955 the highest observed average yearly percentage of blooddonors with ESR 1—2 mm/ 1st hr was 55.3% in 1958; the lowest value was 15.6% in 1974. These fluctuations go parallel with long-term fluctuations of the albumin and antibody content (e.g. γ-globulin) level of the blood.

From 1969 the curve representing the average yearly ESR percentages at Leiden exibited a downward trend until 1974, this was followed by a steep rise at the end of 1974 lasting until at least 1978. A similar trend was observed in Vienna, N hemisphere and in Durban on the S hemisphere. This similarity in trend in the N and S hemisphere suggests that not local but worldwide stimuli control the physico-chemical properties of human blood. In view of the various observations in connection with the Piccardi effect in inorganic colloids it is most likely that such events are caused or triggered by extra-terrestrial forces.

CONCLUSIONS

The present brief review of the many scientific studies undertaken to the present day of the possible effects of extra-terrestrial forces on the physical and biological processes on earth, strongly suggests that, in future biometeorological studies, these possible extra-terrestrial influences should be seriously considered both in the long range planning of climatic changes and in connection with certain biological (particularly cyclic and medical) phenomena, e.g. the outbreak and spreading of worldwide epidemics.

We have seen that many indirect effects of extra-terrestrial solar or lunar phenomena can be explained by changes in light intensity during the night, temperature and food changes in water due to tidal movements, gravity effects in the sea and perhaps in trees. Another important approach is the study of possible direct gravity effects on colloids. In this connection we should like to mention the modern theories on fluctuations in cosmic gravity radiation (Billing, 1974; Dalrymple and Lindsay, 1966; Drever *et al.*, 1973; Editorial in Nature, 1972; Feinberg, 1967; Hines, 1972; Kolmann, 1971; Kooy, 1968; Kundt, 1970; Penrose, 1972, Piddington, 1970; Rahe, 1970; Sciama, 1971; Weber, 1961, 1964, 1970).

Almost 50 years ago Einstein developed his concept of gravity waves with an energy of only 10^{-37} Watt. Weber *et al.* (1961, 1964, 1970), of the University of Maryland, are trying to record these weak fluctuations in our gravity field. Rotating stars and exploding supernovae, the *quasars* (Piddington, 1970) are capable of creating very strong gravity waves which penetrate deep into cosmic space. According to Einstein these waves would propagate with smaller velocities than that of light. However the physicists Feinberg (1967), Kooy (1969) and others believe that small gravity particles, *tachyons*, can pass through space with velocities surpassing that of light and are capable of penetrating all matter. It would be worth studying whether fluctuations in the gravitational pressure in cosmic space are responsible for another group of still unexplainable biometeorological phenomena those put forward in this review paper.

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Newer Methods for Time Series Analysis in Biometeorology

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The variety of meteorotropic phenomena in biometerology requires different statistical methods to confirm the observed relationships between biological, veterinary or medical phenomena on one hand and the impact of meterological stimuli on the other hand. The Chi-square and other statistical methods used in the past are very often inadequate, especially in the case of complicated time structures, such as the so-called '*fluctuating phenomena*', which probably have a very weak cyclic component.

The allotted space is too short to discuss all the aspects of biometerological statistics, which to a large extent have to deal with noncyclic trends. Here, we shall concentrate on such techniques for the analysis of cyclic or semi-cyclic time series which might be used to study the influence of weather and climate in biometerology. The most common aspect of this is perhaps the seasonal fluctuation. The emphasis is on techniques rather than concrete examples from the field.

Cycles evolve in time, together with monotonic trends (e.g. a steadily rising growth curve), and random fluctuations (noise). These are the three main concurring components of any time series. The trend is there because it is difficult to control a real process perfectly over a longer time, the random part because it is unavoidable in any thermodynamic process, and the cycle because most processes are complex enough to contain feedback mechanisms; this usually results in oscillation. Figure 1 illustrates these three components. On addition they produce a typical time series. Notice, however, how similar the composite record is to the random pattern. Both trend and cycle are hidden by the noise – the shorter and the noisier the record, the likelier is such an interaction. A competent time series analysis always identifies all three components separately. Usually the trend is found and eliminated first (subtracted out), followed by elimination of the cycles, essentially by averaging out the noise. (The general idea of statistics is to replace a

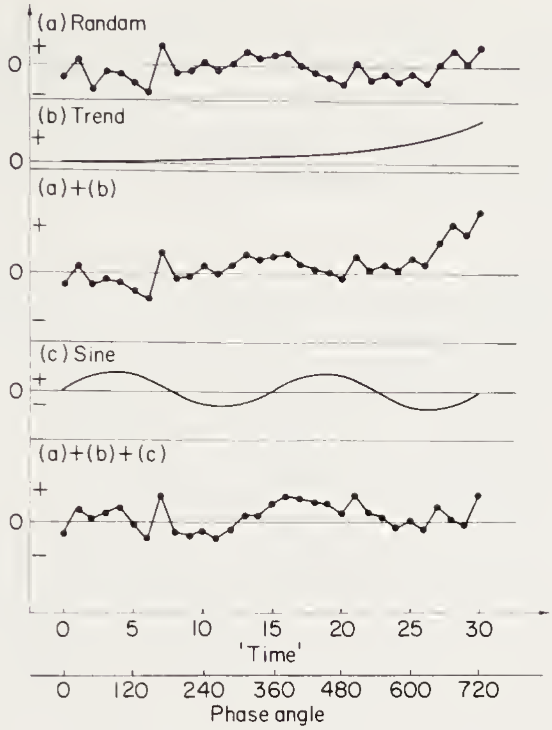

Fig. 1. Time-series model, demonstrating the three main components: trend (b), periodicities (c) and noise (a) (Sollberger, 1970)

bulk of values with a few average descriptors. The averaging 'smoothes out' the noise.) Finally, one subtracts out the cycle, then only noise should be left. Unfortunately, this straightforward procedure is poorly understood by most biological researchers.

It is very seldom that the trend (or baseline) is even mentioned. Yet, unless it is eliminated, the cycle estimate will be wrong, because the component to be averaged out is not random. A trend can most easily be estimated through polynomial curve fitting:

$$y = \mathrm{A} + \mathrm{B}T + \mathrm{C}T^2 + \mathrm{D}T^3 + \ldots \pm E$$

where y = the observed variable and E = the regression residual which will include both noise and cyclic component. The latter cancels out in the calculations owing to symmetry. For this, however, the record should ideally contain one, or several full cycles, otherwise the trend estimate will be wrong. T = time or some appropriate function of time (e.g. log t).

There is an ingenious lagged sampling technique, where trend estimation is crucial because of the long time span. Here, only one observation is done per cycle, each at a different time (e.g. once a day, but one hour later each day).

Some computer packages offer built in trend removal, however, this is often overly simplistic. It is safer to do a separate trend analysis first.

One can also use a moving average (it should span exactly one cycle period), or successive differences between adjacent time points (a linear trend will vanish since the difference is constant, but periodicities will not since the differential of a sine is still a 'sine'). Slow, irregular trend swings caused by systems inertia will also tend to be eliminated by differences.

The difference technique can be expanded by expressing the time series as a set of differences of different order or power, by weighting them, and by adding moving average functions. Such 'autoregressive' schemes represent an exciting approach to time series, used mainly in the prediction of future trends (Box and Jenkins, 1970; Pandit and Wu, 1977). Biological examples are scarce (Reynolds *et al.*, 1976, 1978). The technique is difficult, but worth the effort.

The random residuals are not given enough attention either. Once trends and cycles are fully defined there should only be random variation left. If not, the residuals will still contain trends. The only way of checking is to plot them or study their statistical distribution. Some computer programs automatically list the residuals e.g. BMD03R (Dixon, 1973).

We mentioned that an analyzed time series should always span a full set of cycles, but often the period is unknown. If the series is long, the error will be small; for shorter series the solution is to fit both trend and cycles in one single multiple regression:

$$x = A + B\,(\text{time function}) + C \sin(P + QT) + D\,(\text{harmonics}) \pm E.$$

There should be at least about two periods covered. One cycle, where the period is almost certain, is the seasonal (Gersovitz and Mackinnon, 1978; Lovell, 1963; Sims, 1974). As to the cyclic time series components, there are three basic techniques; multiple regression, autocorrelation, and harmonic (or fourier) analysis. The latter is actually a special case of multiple regression; it yields periodograms and spectra.

Autocorrelation is a remarkable noise eliminating procedure, which can even be used before trend and cycles are sought (Blackman and Tukey, 1958; Box *et al.*, 1970; Kendall and Stuart, 1966; Sollberger, 1976). Pairs of datapoints, N time steps apart (lag) are correlated. Each lag yields one correlation coefficient. If these correlation coefficients are plotted against the lags, the curve (autocorrelation function) reproduces the periodicities. It is however not an exact representation of the cycles. The phase information is lost, and trends are apt to be misrepresented. There are also three different formulae for the correlation coefficient to choose from. All in all, however, the function still gives a concrete picture of the data behaviour, the spectrum does not. One should study both and present both in the published paper. (Figure 2 illustrates the method; compare the short example of original data with the autocorrelation.) A related procedure is crosscorrelation, where two

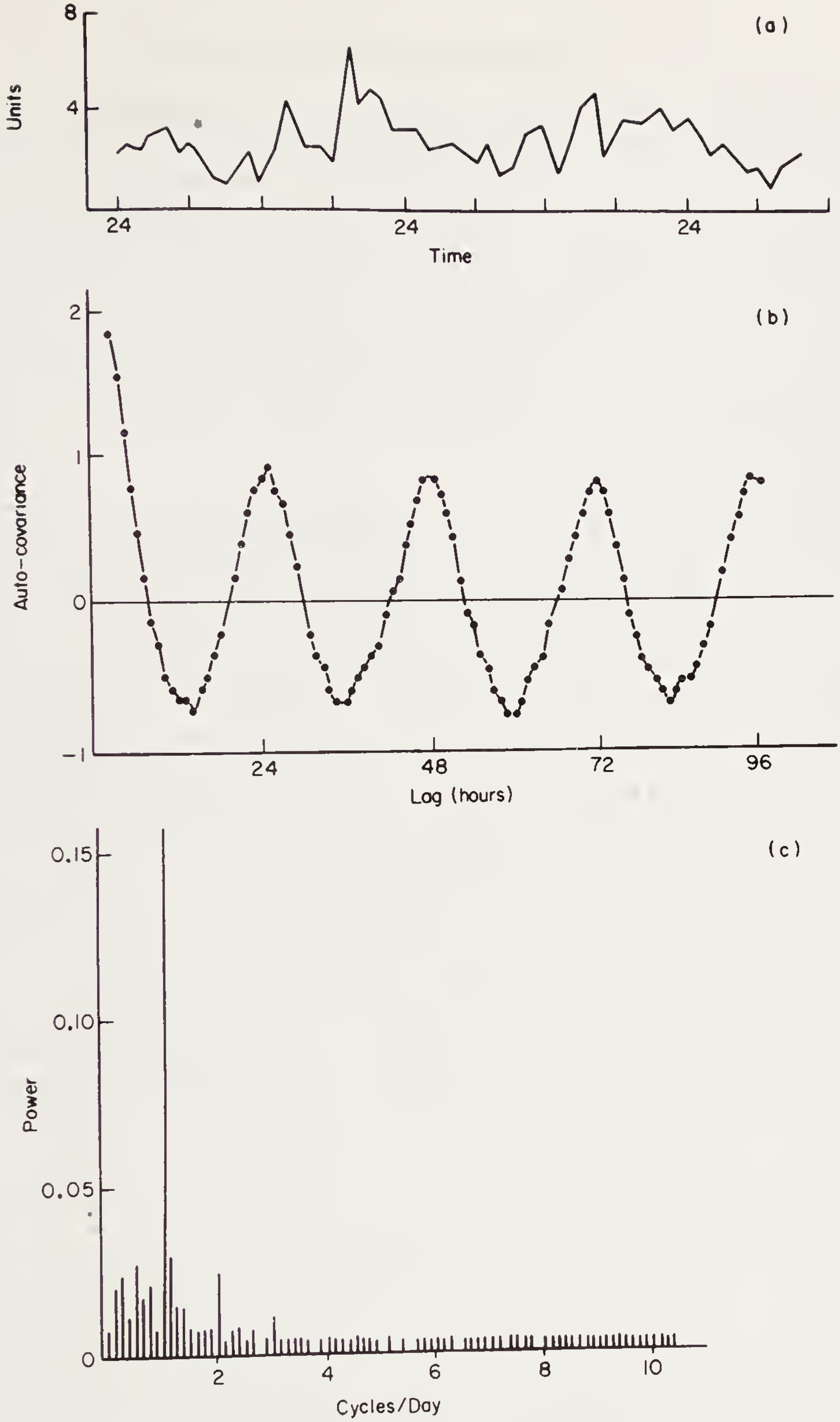

Fig. 2. Example of power spectral procedure. Bird activity every 15 min over 26 days in constant environment (light, temperature). Experiments performed at the Highland View Hospital, 1964 (Sollberger, 1970, 1976).

(a) Example of original record.

(b) Autocorrelation function (after detrending). Computations by Dr. Paul H. King.

(c) Power spectrum. Computation by Dr. Paul H. King.

((b) and (c) are from Sollberger (1970) with permission of the publishers.)

different data series are lagged, instead of one series with itself. It pulls out the common trends in the compared series.

The harmonic analysis can be done on either the original data or the auto (or cross) correlation function. The computations are simple (Sollberger, 1970), so that one can fit large numbers of sines, which is not possible with multiple regression. The data must, however, cover a full set of cycles, and the sampling must be equidistant in time, else regression must be used. On graphing the results, one plots the magnitude of the various sine components against their frequencies. Various representations of the magnitude can be used; the amplitude, its logarithm, or its square (power).

There are many variants of harmonic analysis. Let us, for simplicity, distinguish between power spectra, amplitude spectra, and periodograms. The amplitude spectrum would be a strict harmonic analysis of the original (but detrended!) data. The power spectrum does first an autocorrelation, then a harmonic analysis of that function (see Fig. 2c). Both demand that all the fitted sines be harmonics of one basic sine (usually defined by the total data span). Harmonics are mathematically independent, so that each *bar* in the spectrum can be judged statistically on its own merit. (There are error estimates which can be used, though they are rather wide; Blackman *et al.*, 1958.) As with the autocorrelation, however, there are interpretation problems. For this reason, it is safer to study both. Spectra works best with long series; the less any cycle stands out, the longer the time span needed. If a cycle really dominates, perhaps even 10 cycles might suffice. But then, of course, very few harmonics can be obtained (poor resolution).

Another limiting factor is the temporal sampling interval. By design, it represents a cycle which is imposed upon the series, and may interfere with its true cycles (aliasing), creating artefactual new frequencies. One should, therefore, have a reasonable number of data points per cycle.

If the data cycles are not really sinusoidal in shape, the spectrum will still report with sine amplitudes. In principle, however, any departure from the '*ideal*' shape will appear as a set of harmonics and the basic cycle period will still be correctly represented. This means, though, that the presence of a 'significant looking' harmonic may not necessarily imply that such a cycle entity is operating in the studied system. Another poorly understood fact is that the frequency estimates in the spectrum are biased, as soon as the total time span is not an exact multiple of the true (often unknown) cycle period (a 24-h component, say, might therefore really represent a circadian 24.6-h cycle).

If the dataset is small there are other methods which explore the data more efficiently, *viz. regression analysis*, or even *simple periodograms*. The latter still fits sine curves. (There are many variants of the technique: see Chronobiologia or the International Journal of Chronobiology.) The sines need not form a harmonic set, therefore one data cycle will no longer be represented by one amplitude, but by a hump. Neighbouring amplitude estimates are no longer statistically independent. They 'lend' power to each other. Figure 3 shows an example.

This approach is related to the even more basic *array analysis*, where the time series is cut up into contiguous equal segments, which are superposed. Their average curve will have a certain vertical range, analogous to a sine amplitude, and the total variance of the curve-set will approximate the spectral power. One then varies the length of the segments, and obtains a periodogram by plotting variance against segment length (Enright, 1965a; Sokolove and Bushell, 1978). Common statistical tests (e.g. the analysis of variance) can then be applied. However, these tests will not change if the values were to be shuffled along the time axis and do thus not yield any proof of periodic structures – sine curve fitting. One advantage is that no particular cycle shape need be preassumed; instead one can try to fit various curve models to the average curve with the largest variance (Winget *et al.*, 1969).

An exciting development is the use of *factor analysis* (Harman, 1967; Basilevsky and Hum, 1977). In its usual form it is applied to a set of measured variables and yields a new set of different, linear, independent combinations of the variables, called factors. If the variables are now replaced by sets of successive time values, each factor will describe a curve which should represent an independent time series component. Periodicity need not be implied. The analysis can be performed on the autocorrelation function (which will emphasize periodic functions) or on arrays. The latter approach was used on behavioral observations of wild, caged falcons by one of the authors (Nunn). The frequency of preening was counted over successive five-minute periods throughout several days. If plotted versus time, the

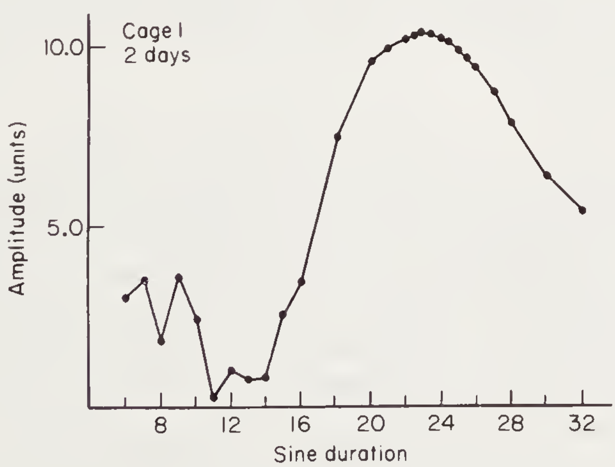

Fig. 3. Periodogram of startle response from six rats, elicited every hour throughout 48 h. Sollberger and Davis, 1972). A log trend was removed before fitting.

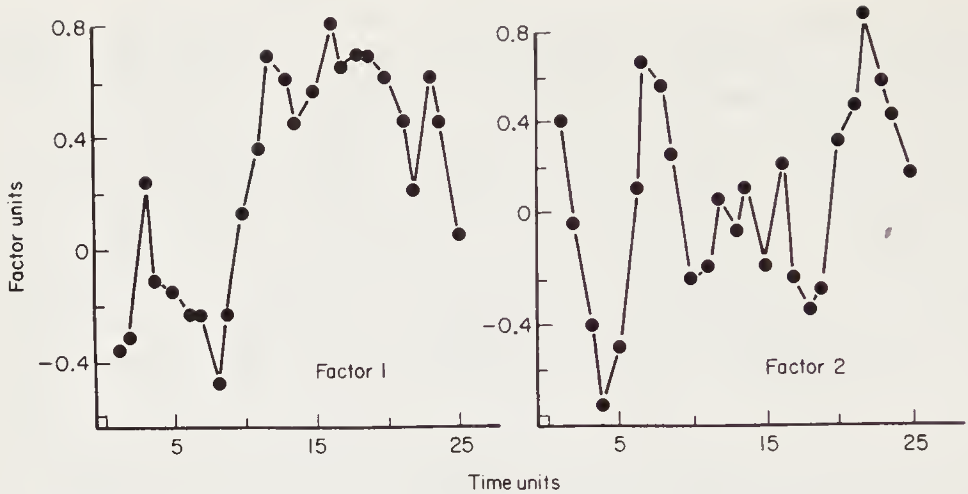

Fig. 4. Temporal factor analysis of preening behaviour in a falcon (Nunn). Two first factors. Factor 1 reproduces typical 'bout'-structure. Data contained 10 about 125-minute bouts; cf. text. The factors are here represented by the principal components in the analysis. One time unit = 5 min.

frequency displays complex structures — about 125-min bursts separated by variable, quiescent intervals. Each burst cycle has a complicated shape, including one smaller and one larger peak. The superposed burst cycles from a full day yielded the configurations in Fig. 4. The first component shows a typical burst structure; the second component is quite different, almost inverse to the first. These t o accounted for the largest part of the data variance. The interesting question is how many and which components might represent true temporal behavior structures.

It would be ideal if one could also fit non-sinusoidal shapes and use continuous, periodic functions. This can be done in the regression domain, through analogues to the amplitude modulation used in communications theory. One of the authors (Sollberger, 1977) has tried the function:

$$y = C + A.\mathrm{F}(TS).AM.\ \sin\,(P + QT)$$

where, T = regular time, TS = time counted sequentially within a sine but reset to zero for each new sine (an analogue of the internal phase angle); AM = sine amplitude; C = the mean (sine level); $\mathrm{F}(TS)$ is some arbitrary function of 'sine time'; A = the regression coefficient.

By defining $\mathrm{F}(TS)$ as a polynomial of TS, applying classical harmonic decomposition and rearranging some terms, one gets:

$$\begin{aligned} y = {} & C(0) + C(1, 1)TS \sin\,(T) + C(1, 2)TS \cos\,(T) \\ & + C(2, 1)TS^2 \sin\,(T) + C(2, 2)TS^2 \cos\,(T) + \dots \\ & + C(\mathrm{N}, 1)TS^{\mathrm{N}} \sin\,(T) + C(\mathrm{N}, 2)TS^{\mathrm{N}} \cos\,(T) \pm E. \end{aligned}$$

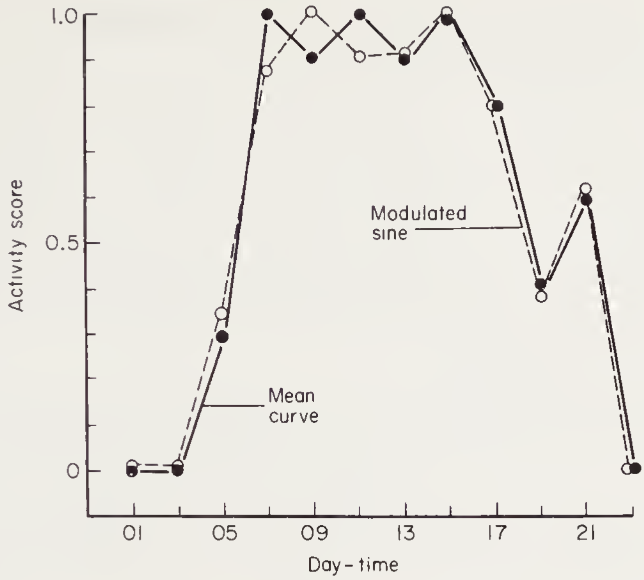

Fig. 5. Fitting modulated sine (Sollberger) to activity data from one institutionalized older person. Ten consecutive 24-h cycles, measured every second hour. 24-h sine modulated by fifth degree polynomial of time within each sine (internal phase angle analogue); cf. text (data from Wessler *et al.* 1976).

Phase and amplitude estimates, as well as regression coefficients have merged into coefficients C.

Figure 5 shows an example, comparing the array mean curve of 10 circadian cycles with the above function fitted to the fifth polynomial degree. The method can be extended to include special analogs and iterative fitting. Other functions of the sine are being tried.

If one wants to maximize the information obtained from the data, the next step is to fit a cycle to one period (or even less) at a time. Blume (1965, 1978) does this. Such methods are time consuming but allow one to catch small shifts in the cycle parameters over time. One can graph each cycle as a point in the polar diagram using vector addition. This will produce beautiful vector trajectories (Winget and Leach, 1977).

A field for statistical development is the mathematical modelling of environmental cycle control. There are many different models, and new methods are needed to compare them. The approach allows functional modelling (Kaiser, 1977; Pavlidis, 1973; Pittendrigh, 1965; Wever, 1963, 1972; Winfree, 1976), which pure statistics does not — for instance expressions for the stability of a cycle against environmental influences. An example is the increased study of limit cycles.

An interesting development is the growing acceptance of a variability in the solar constants and the possibility that these might be influenced enough by planetary movements to transmit effects to our biosphere, perhaps through a modulation of the sunspot radiation. To avoid un-sound speculation, such a subject must be cautiously approached. This involves the use of efficient statistics.

While the sunspot cycle has been extensively and competently analyzed, the same cannot be said for possible lunar-biological (and planetary) effects. Array analysis and frequency counts are commonly used for selected events at different positions in the postulated external cycles. Usually, only one array is prepared; as mentioned, no statistics can prove periodicity for this. Since the array period is not varied, there is also no test of whether the observed and the environmental cycles really have the same period.

These authors should realize that there are powerful spectral and regression methods available. Planets have known periods which can be entered into a regression. Several of these can be fitted simultaneously. Special interaction terms, dummy variables and qualifiers can also be entered to create an unlimited scope for statistical exploration. Until such methods are tried, the scientific community will remain skeptical.

A practical problem most chronobiologists nowadays face is to explain the so popular '*biorhythms*' to the layman. According to this theory, each individual is endowed with three cycles which start at birth and run unerrantly throughout life. They represent different aspects of personality with periods of 23, 28 and 33 days. Obvious comments, of course, are that no biological cycles of such accuracy have been observed, that two of the cycles have no environmental correlates which might synchronize them and account for the postulated precision and that neither have they ever been actually observed in any biological variable.

There is, however, a subtle statistical problem involved which most people are not aware of and that is the effect of the natural cycles on this construct. We have both the female menstrual cycle and the monthly (or multi-weekly) social cycle. Though variable, they average out close to 28 days, lending power to the exact postulated frequency of 28 days and to the other two postulated cycles. If one, therefore, uses the three cycles to predict the fate of a person and then compares this with the actual outcome for that person, and if one does this on a huge (random) database, a statistically significant agreement will be found if tested with (say) a Chi-square (the approach usually chosen). This 'significance' is nevertheless spurious. For the same reason, spectral analysis will fail. Again, a correct approach would entail advanced regression analysis.

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