configurations are of limited size, and are built up from a limited number of basic units, their possible variety, though large, is finite. Various workers have suggested that the number of different antibody specificities is limited. HAUROWITZ[11], estimated that not over 50,000 different antibodies exist, and TALMAGE[12] proposed making do with 5,000.

The specificity of a lectin is evidently due to the fact that one or more (usually several, it seems) of its surface configurations is complementary to a configuration that occurs one or more times on the surface of a polysaccharide or a protein molecule. It is not to be expected that a lectin will possess a configuration complementary to a configuration that appears in all polysaccharides or all proteins, which might make it indeed nonspecific.

These arguments are supported by several lines of evidence: The work of KABAT[13] indicates that the specific determinant groups of polysaccharides are made up of only about 6 monosaccharide residues. The complementary configuration in the corresponding antibody or lectin would therefore be of similar size. LANDSTEINER's experiments with di-, tri- and polypeptides as haptens[14] indicated that polypeptides containing 5 or 6 amino acids were about as large as the antibody-forming mechanism cared to recognize as a single determinant. SPRINGER and DESAI[15] found the specific determinant recognized by the anti-H(0) lectin of the eel to be a portion of a single monosaccharide. It is hard to believe that the specifically reactive structure in this lectin is very complicated.

The specifically reactive groups in other lectins likewise seem to be of limited size. MATSUBARA and BOYD[16-19] found that relatively minor chemical alteration of a lectin could alter its specificity considerably. They found[18] that phenylazobenzoylation of the Lima bean and *Sophora japonica* greatly increased the anti-A activity. Examination of pronase digests of these modified lectins showed that the peptide containing the PhAB residue was composed of only 3 or 4 amino acids: not proof, to be sure, but suggestive.

ETZLER and KABAT[20] found that the purified lectin of *Dolichos biflorus* was specific for α-linked D-GalNAc, although they did not establish the exact size of the complete reactive group in the antigen, and HAMMARSTRÖM and KABAT[21] found that the purified lectin of *Helix pomatia* precipitated with macromolecules having terminal α-linked D-GalNAC, but not with those having β-linked D-GNAc end groups. PORETZ and GOLDSTEIN[22] reported that in the purified concavalin A molecule there are present binding loci complementary to the 1,5-anhydro-2-deoxy-D-arabino-hexitol or the arabinofuranosyl ring systems. All these observations combine to suggest that the specifically reactive group in the lectin is relatively small.

Considering all of the above facts, I venture to suggest that, aside from purely physical chemical processes such as the precipitation of proteins with normal isoelectric points by the basic histones, there are no nonspecific large molecule-large molecule interactions.

Zusammenfassung. Es wird diskutiert, ob die Wirkung pflanzlicher Hämagglutinine als spezifisch oder unspezifisch zu bezeichnen sei und festgestellt, dass eigentlich fast alle Reaktionen zwischen Molekülen mit grossem Molekulargewicht spezifisch sind.

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3 September 1974.

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THEORIA

The Possible Effect of Meteorological Stress on Cancer and its Importance for Psychosomatic Cancer Research

In any adult multicellular organism there is a close interrelationship between cell growth, cell metabolism and the state of the central and autonomic nervous systems. Disturbances in the nervous balance are reflected in hormonal disturbances causing a dysfunction of enzymatic mechanisms, tissue functions, antibody formation, etc. It could affect also the histological structure of nerve ganglia and fibres (KHAZANO, 1937).

Experimental studies, particularly in the USSR (PETROVA, 1945; KAVETSKY, 1951; KAVETSLY, TURKEVICH and BALITSKY[1]) and in the USA (e.g., CORSON[2]) have shown that disturbances in the higher brain centres could trigger and accelerate neoplastic diseases. Several physiological mechanisms are involved.

Overstimulation of the brain centres and of the cerebral cortex creates a weakening of the cortical functions, affecting the thermoregulatory function of the hypothalamus, the functions of the rhinencephalon or emotional brain (PRICK[3]), of the pituitary, thyroid and adrenal gland and of the thymus, essential for the production of lymphocytes and development of adequate

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immunological responses by the body against antigens (METCALF, 1966), for example cancer specific antigens as described by MAKARI, 1955. But also the pineal gland or epiphysis is affected. This photoperiodic brain is a neurochemical transducer which regulates the timing of physiological events and is therefore responsible for many endogenous biological rhythms (WURTMAN, AXELROD and KELLY[4]).

Many physiological studies have shown that each of the physiological centres described are affected both by psychological and meteorological stresses[5]. Both types of stress trigger the same physiological mechanism in the human body and therefore there is no reason to assume that meteorological stresses would not affect neoplastic diseases in a similar way as in the case of psychological stress. This observation facilitates the study of psychosomatic cancer phenomena by means of biometeorological experiments.

Main meteorological parameters affecting the human body and the principle physiological centres through which these stimuli are recorded. Several meterological factors could affect the normal physiological processes in the human body: Thermal stimuli (both heat and cold and particularly combined with wind effects, so called cooling index), solar radiation (both IR heat radiation with 780–7300 nm wavelength and UV-radiation, with < 290–380 nm wavelength), humidity, air movement, reduced partial oxygen pressure (high altitude effects), electric properties of the atmosphere (ionization, electromagnetic long waves with wavelength 6–100 km and the electrostatic potential gradient), air pollutants etc. These stimuli are registered by the human body through the skin, the respiratory tract, nose, eyes and directly by the nervous systems. The Table gives a summary of the most important meteorological effects caused by the abovementioned meteorological stimuli.

One of the principal structures in the brain through which changes in weather and climate effect the body is the hypothalamus, the principal heat regulatory centre[3].

Registration of changes in environmental temperature probably takes place as a result of minor alterations in the physico-chemical state of the blood circulating through the rich network of hypothalamic capillaries. At the same time the hypothalamic nuclei receive information from the thermal receptors in the skin. VOGT, AMIN et al. showed that noradrenalin and 5-hydroxytryptamine (5-HT) occur in very small concentrations in the hypothalamus; DOMER, FELDBERG, MEYERS et al. found that excess of free 5-HT or catecholamines in one side of the anterior hypothalamus seemed to be a factor determining the level of body temperature.

The effects of meteorological stimuli are different during different periods of the day (biological rhythm effect). They depend also on the previous physiological history of the subject (law of Wilder), the experimental history (socalled ontogenetic age of DENENBERG[6]), the degree of acclimatization to the physical environment, the psychological and anatomical typology of the subject, age, sex etc.

It could be demonstrated (TROMP[3]) that if a subject is subjected to meteorological stress during 1 h per day only and he spends the rest of the day in a constant physical environment, the physiological pattern due to a short meteorological stress will continue for a considerable time.

Apart from thermal stresses also sun radiation plays an important role. Solar radiation affects the skin but also the pituitary and hypothalamus through indirect stimulation of the eye nerve and other radiation receptors of the body (BENOIT, MILINE and HOLLWICH effect).

Through the intermediary of the hypothalamus long lasting meteorological stresses could have a profound influence on the hormonal processes in the human body. This could affect carcinogenic processes. Many hormones have growth stimulating effects. For example it is known that thyroid tumours could be caused by an excess of thyrotropic hormone, tumours of the adrenal cortex by adrenocorticotropic hormones etc. These various hormonal processes are seriously affected by a dysfunction of the thermoregulatory centre in the hypothalamus.

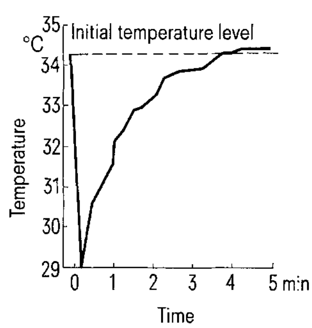

Fig. 1. Thermoregulation curve of a normal, well thermoregulated subject.

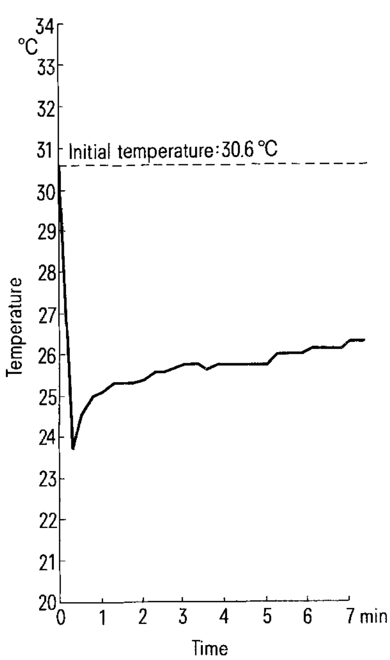

Fig. 2. Rewarming curve of a male subject of 23 years, suffering from inoperable rectum carcinoma.

[4] R. J. WURTMAN, J. AXELROD and D. E. KELLY, *The Pineal* (Academic Press, New York 1968).

[5] S. W. TROMP, *Progress in Biometeorology*, Part IA (Swets and Zeitlinger Publishing Co., Amsterdam 1974).

[6] i.e. The relationship between stimuli received during infancy and the later adult emotional reactivity, which is affected in animals by maternal-infant relations, material parity, litter size, neonatal hypothermia, neonatal handling etc. (Psychol. Rev. *77*, 335 (1964).

Thermoregulatory efficiency of cancer patients. In 1964 TROMP and BOUMA[7] studied the thermoregulatory efficiency of cancer patients in the Antoni van Leeuwenhoek clinic in Amsterdam, using the water bath test of TROMP[8]. After previous adaptation to room temperature the left hand of the subject is submerged in water of 10°C for 2 min and quickly dried. The rise in skin temperature of the palm of the hand recorded every 15 sec is represented in Figures 1 and 2. It was found that the general thermoregulation efficiency of cancer patients is very poor (see Figures 1 and 2). The seriousness of the cancer case is clearly reflected in the inefficiency of the rewarming curve during the water bath test.

In view of the great influence of meteorological stimuli on the thermoregulatory function in man and considering the considerable effect of hypothalamic stimulation on the hormonal functions in the human body (through pituitary, thyroid and adrenal gland) it seems logical to assume that meteorological (in particular thermal) stresses could affect cancer development.

Previous reports on the influence of thermal stimuli on cancer development. Several research studies seem to support this assumption. Interesting studies were carried out by LEA[9]; LEE[10]; MCVAY[11]; KRASNOW[12], GLASER and AUSTIN[13]; DE SAUVAGE NOLTING[14]; POMP et al.[15] and others.

Studies by LEA. LEA[9] studied a possible association between death rate from cancer of the breast in females and the mean annual temperature in Norway, Sweden and Great Britain. It was found that a highly significant correlation ($p < 0.001$) exists between breast cancer and mean annual temperature.

Later studies using 33 countries confirmed this observation, although in 6 countries the relationship was missing. Further support for the assumption, that this finding is not due to an artefact, is the fact that no latitude effect could be established for death rates of the uterine cervix and of the body of the uterus.

Studies by MCVAY. MCVAY[11] found a similar correlation in 32 countries between death-rate for malignant neoplasms of the intestinal tract (including colon and rectum carcinoma) and the mean annual temperature.

Studies by LEE. LEE[10] pointed out that there is a pronounced seasonal incidence in the case of mortality from malignant disease, which may be partly due to the general deterioration in health of older people during winter. In England and Wales, during the period 1950–1962, there was a death-excess of about 4% during October–March as compared with April–September. This winter excess amounted to 6% in the case of breast and lung cancer and 2% in the case of stomach cancer. However, in some types of cancer tumours there is a summer excess. It is also interesting that the seasonal effect observed in England occurs in Australia and New Zealand but 6 months out of phase.

Studies by KRASNOW. KRASNOW[12] started a study based on two observations: 1. The observation of Landsberg (1969) that areas of low malignant death rates, as shown on a U.S. county-by-county map of KRASNOW, are areas of low wind velocity; 2. the observations by TROMP and BOUMA[16] that many diseases characterized by an inefficient thermoregulation of the patient usually correlate with the degree of atmospheric chilling.

A study was carried out by KRASNOW for 50 countries in the USA, 25 with highest and 25 with the lowest death rates of cancer of the digestive system, breast and respiratory system. It was found that malignancies of the large intestine and rectum, digestive system, stomach and breast showed a statistically highly significant negative correlation with temperature. On the other hand, the respiratory system (lung, trachea and bronchus malignancies) showed a direct relation with temperature.

Studies by GLASER and AUSTIN[13]. YOUNG demonstrated the effect of temperature on induced mammary tumours in rats. They are less frequent at 5°C than in an environment of 32°C. According to GLASER and AUSTIN[13b] inplanted Sarcoma 180 tumours in mice are smaller in those kept at 8°C than those kept at 22 or 33°C. There is a linear correlation between environmental temperature and the weight of Sarcoma 180. GLASER and AUSTIN[13a] also studied the effect of protamine sulphate applied at different temperatures. The tumour growth was more retarded at 8°C as compared with the effects at 22 and 33°C.

Studies by DE SAUVAGE NOLTING[14]. Already in 1956 DE SAUVAGE NOLTING[14] observed, after correction of the average monthly birth frequency of the total population in The Netherlands, seasonal fluctuations in birth dates in a group of 1510 cases of cancer. Most cancer prone subjects were born in winter, in particular in the period December–March. Lowest values were found in June–July; 1242 cancer cases collected by KEOGH in Australia showed the same phenomenon, only with a 6-month shift as compared with the northern hemisphere. In other words, most cancer-prone children in Australia were born in June-July. Identical results were obtained in 1961 in 15,091 cancer cases in The Netherlands. The seasonal difference was highly significant ($p < 0.001$). This seasonal variation in frequency of cancer birth months was confirmed by STUR[17] using 2,829 cases. It was also found by DE SAUVAGE NOLTING in 1,336 cases of pulmonary carcinoma collected by ALLEN[18] and in 326 cases of lung cancer described by DIJKSTRA[19]. BOOT[20] observed in mice of the C_3H strain, known for its high incidence of mammary carcinoma and kept at the Antoni van Leeuwenhoek Cancer Clinic in Amsterdam, that in mice born in winter the cancer incidence was 12% higher than in summer.

Studies by POMP et al.[5]. It is known both from experimental and clinical work that very high temperatures during hyperthermia have a retarding effect on the growth of malignant tumours. POMP et al.[15] applied these findings clinically in Germany and Austria. The hyperthermia was created by 11-m short waves in a cabin with an air temperature of 70°C during 2 h. It was applied to breast and lung cancer. The retarded growth observed is probably due to the raised tumor cell metabolism, changed enzyme activity and antibody system as a result of the hyperthermia.

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Principle centres* of the human body registering meteorological stimuli

I Skin	II Lungs and throat (Respiratory tract)	III Nose	IV Eyes	V Direct effects on the nervous syst.
1 Thermal effects through conduction, convection or infrared radiation recorded by thermoreceptors in skin and hypothalamus, effects counter-balanced by vasodilatation or constriction or sweating. Effects on: a) Hormonal functions of pituitary (anti-diuretic, thyrotrophic and gonado-trophic hormones), thyroid and adrenal gland (17-keto-steroids) and pancreas (insulin production and blood sugar level). b) Blood: changes in albumin and globulin levels and blood cells composition. c) Electrolyte balance Cold stress decreases excretion in urine of chloride, sodium, urea, hexasamines, rise in pH. d) Liver function (transaminases and hepatic metabolism) e) Other physiological processes affected by a)–d) 2 UV-radiation effects: a) Melanin oxidation b) Increased vit. D and histamines in skin. c) Increased gastric acid secretion. d) Blood: increased haemo-globin, Ca, Mg, and phosphate level e) Protein metabolism (increase) f) Hormones: thyroid (hyper-thyroidism) and adrenal gland, gonadotrophic functions g) Direct lethal effects on bacteria (indirect effect on man) h) often lowering of reaction speed 3 Changes in acidity of the skin (Marchionini) a) by aerosols b) by factors affecting sweat production and evaporation.	1 Temperature and humidity: Affecting mucous membrane Dry air a) drying and decreased elasticity of mucous mem-branes (leading to micro-fissures) and decreased ciliary activity (inefficient removal of dust) b) decreased mucous (and anti-body) production c) decreased bloodflow and warming up of inhaled air Cooling a) decreased permeability of membrane b) constriction of blood capillaries. Affecting survival of bacteria and viruses 2 Ionisation: Surplus of negative ions causes (acc. to Krueger): a) Increased ciliary activity (from 1100–1700/min) b) Increased mucous production due to oxidation of seratonin enzyme in trachea. 3 Acidity of the air a) pH $>$ 8.0: increased permeability, inflation of mucous membrane cells, decreased ciliary activity b) pH $<$ 7.0: shrinkage of cells c) pH $<$ 5.0: bronchitis complaints d) throat mucous usually acid only in 8% alkaline 4 Decreased partial oxygen pressure a) increased lung ventilation b) increased adrenal activity c) increased heart and puls rate d) changes in composition of blood cells e) increased peripheral blood-circulation f) increased thermoregulation efficiency g) increased bloodcirculation in brains h) improved autonomic functions 5 Increased partial oxygen pressure Treatment of gas gangrene and (anaerobic diseases) phlegmone 6 Trace elements a) Ozone: In low concentration killing bacteria, in high concentration irritating mucous membranes and increasing infections b) Salt (NaCl) Fine aerosols with $^1/_4$–$^1/_2$% hypotonic salt solution ($<$ 0.9% NaCl) cause swelling of mucous membranes. Hypertonic solutions cause shrinkage. 7 Airpollution a) Gases: (SO_2, CO_2, benzpyrene etc.) b) Particles: (1) organic (pollen, spores) causing allergic reactions (2) inorganic: mineral dust (silicosis etc.) c) Aerosols: Strong increase of physico-chemical action due to increased action surface of small particles and their electric charges	1 See effects on lungs and throat. 2 Direct stimulation of alfaetory-brain (rhinencephalon), affecting mood, cardio-vasomotoric, visceral and endocrinal activities. 3 Acidity of nasal secretion normal values pH: 5.5–6.5. pH affects membrane permeability. pH lowers with rest, heating of nose, diluted acetic acid sprays, sleep, acid vasoconstrictors Also saliva more acid at night. pH rises during rhinitis Acc. to Tweedie with pH 6.5 or lower, negative bacterial cultures.	1 Direct overstimulation of the eye causing inflammation 2 Light-flickering of certain frequencies activating epileptic attacks. 3 Benoit-effect on pituitary (gonadotrophic effects) confirmed by MILINE 4 Complete darkness causes changes in carbohydrate meta-bolism, urine volume, blood sugar level, reduction in size of pituitary, affecting thyroid and adrenal gland (Hollwich-effect). 5 Acidity of the mucous membrane surface of the eyes. important for hordeolum, blepharitis, conjunctivitis, etc.	1 Electrostatic (pulsating) and electromagnetic fields: affecting bees (SCHUA, BECKER, HAINE and KÖNIG), golden hamsters (SCHUA), nerves (GENGERELLI, THOMPSON), reaction speed (REITER), plant growth (MURR) 2 Microseismic effects (ampl. 1–20 μ and freq. 6–8/sec.) on eel (DEELDER) 3 Direct stimulation of olfactorybrain (see sub. III) 4 Rohracher effect mechanical fibrations of the human body with frequencies 6–12/sec.; ampl. 1–5 nm Freq. increases with increased thyroid activity or fever to 14; it disappears after death. It is absent in poikilotherms.

* Note 4: Gravity field effects: Studies by BANCROFT, BRINEY, BURTON, COOKE, KELLEY, SMITH, WUNDER a.o. suggest that accelerative forces for a few min to several days cause growth modifications in mice, hamsters, birds, etc. 10–11 day exposure of mice to 2 g forces causes increase in heart weight (as compared to body weight), weight reduction of the spleen, lowered hematocrit and hemoglobin content, increase in number of phagocytic neutrophils, reduction in rate of body weight gain, etc.

* Note 1: Radon effects. Studies by Engelmann suggest biol. effects by inhaling radon aerosols ($<$ 80 Mache U.) or drinking radon water (800 MU/L); stimul. of cell functions, oxidizing processes, lowering of Syst. B.P., dilata-tion of periph. arteries, acceleration of endocrines.

* Note 2: Magnetic effects Strong ($>$ 1500 Gauss) constant magnetic fields seem to affect cell-rotation, growth of animal tissues, pain-deadening influence, cancer development etc. (see S. W. TROMP; *Psychical Physics*, 1949 p. 264–282).

* Note 3: Cosmic rays effects Recent studies by F. H. J. FIGGE (1947), J. EUGSTER (1951), S. G. ONG (1962) and others suggest direct biological effects at cellular level due to Cosmic rays.

Influence of high altitude climate on cancer development. In the Table some of the major physiological effects of high altitude treatment have been summarized. WARBURG[21] exposed cancerous rats to a gas mixture, containing 5% oxygen, for 40 h simulating an altitude of 12,000 m. The tumours became markedly but not completely necrotic. The experiment was repeated by CAMPBELL and KRAMER[22] at a simulated altitude of 5,100 m. Rats were kept alive for 2 weeks. The tumours did not regress but the growth was markedly inhibited. SUNDSTROEM and MICHAELS[23] observed regressions in Walker tumours in all experimental series kept at 360 mm Hg atmospheric pressure (about 6,000 m altitude). The average regressional rate as compared with controls was 39%. Under 300 mm Hg it was 45%. The effect is explained by the authors by stimulation of the adrenal function by reduced oxygen pressure at altitude[5], changing the level of corticosteroids in the blood serum. Also the observed increase in calcium in necrotic tumours and the decrease in calcium content of livers during reduced atmospheric pressure may be involved. The importance of the adrenal gland is suggested by the fact that adrenalectomy of tumour-bearing rats stops further regression after low pressure treatment. In fact the tumours start growing again.

Influence of different complex meterological conditions on growth of transplanted tumours. UNGEHEUER, BREZOWSKI, WRABA and RABES[24] studied the causes of fluctuations in the number of rats in pure strains of rats in which no cancer development occurred after tumour transplantation. 737 rats of the Walker carcinoma strain were studied during the period June 1961–June 1963. It was found that the number of non-resistant animals was smallest during quiet high pressure atmospheric conditions. The number increased during the approach of cold fronts and dropped again after the front had passed. The observed differences (67 and 79%) were statistically significant. The effect is greatest when the meteorological stimulus takes place 1 or 2 days after the tumour transplantation.

Possible effect of meteorological factors on viruses. The increasing evidence that leukemia and various types of cancer[25–27] may be caused by certain carcinogenic viruses is another aspect of possible meteorological effects on cancer. Various biometeorological studies (TROMP[3]) have shown that virus development depends on certain critical boundaries of temperature and humidity. Meteorological factors influence also the general resistance of the body against infections and the permeability of membranes. They also affect the antibody level of the serum[28]. It is therefore not excluded that soil, weather and climate could influence carcinogenic processes induced by viruses.

Conclusion. The various physiological mechanisms described, which are triggered by meteorological stimuli, may help to explain the effect of psychosomatic factors on cancer[29]. Whereas in purely psychosomatic research it may be difficult to study the real mechanisms involved, biometeorological studies on the effects of meteorological stress may assist future psychosomatic cancer research.

Various studies suggest the great influence of thermoregulatory processes on the hormonal functions in the human body. Disturbance of these processes may lead to cancer development. Experiments by TROMP and BOUMA have shown the very poor thermoregulatory efficiency of cancer patients. Studies by LEA, LEE, MCVAY, KRASNOW, GLASER, DE SAUVAGE NOLTING and others confirm the effect of meteorological stresses (in particular thermal stresses) on thermoregulatory processes and cancer development. The similarity in physiological processes during meteorological and psychological stresses may facilitate the studies on the influence of psychosomatic factors on cancer.

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PRO EXPERIMENTIS

An Electronic Method for Measuring the Heart Frequency of the Waterflea: *Daphnia pulex*

So far relatively few researchers have explored the possibility of employing invertebrates for testing drugs. Two of us (R.N. and G.N.) students of the HTS in Heerlen, had to prepare a synthesis of phenobarbital and compare the synthetic with a commercial product.

In a preliminary research, *Daphnia pulex* appeared to respond specifically to a number of drugs and hormones. We have found that the following altered the heart frequency of the water flea: oxytocine ADH, cAMP, acetylcholine, triiodothyronine. With phenobarbital there is a sharp decrease in heart frequency. In this study a clear correlation was found between heart frequency and phenobarbital concentration, which allowed us to test the 2 different phenobarbital preparations mentioned above. A special technique was devised to measure the heart frequency.

Materials. The apparatus used is shown in Figure 1a. It consists of: 1. A projection microscope type: Ken-A vision model Tech-A, lamp: 100 W 1A/GE. 20 V 5A/G $16^1/_2/3$.; lenses: objective N.A. 25, ocular 8× and 10×. 2. To maintain a constant temperature, a heat absorber is placed between the animal specimen and the projection lamp. The heat absorber is a saturated solution of $CuSO_4$, chilled with ice, which keeps the specimen temperature constant within 0.5°C for a maximum period of 10 min. 3. A light dependent resistance (LDR) connected to an amplifier (Figure 2), 4. A source of direct electrical current: 2 nine volt batteries connected in series. 5. An oscillo-