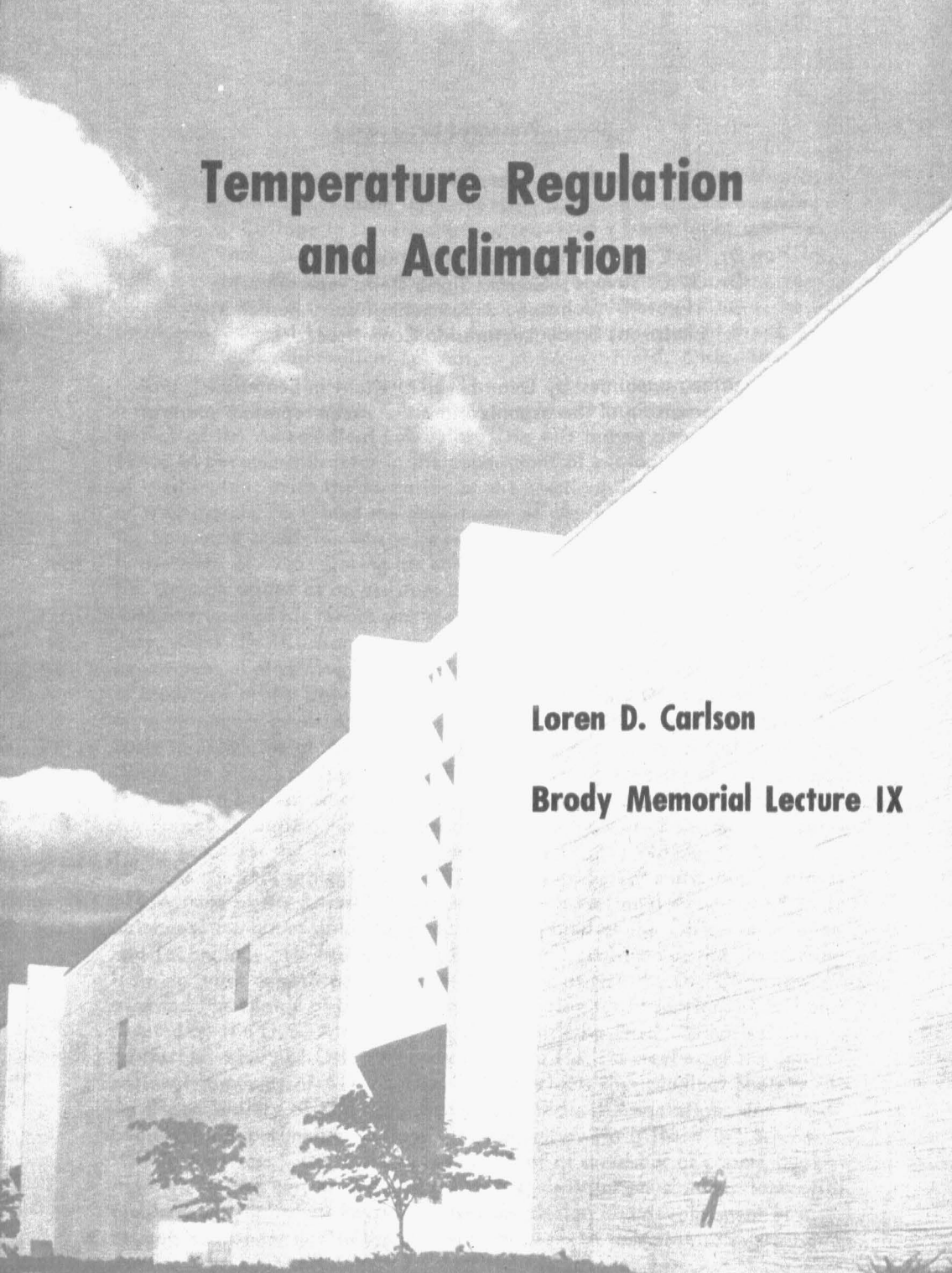
Temperature Regulation and Acclimation

Loren D. Carlson

Brody Memorial Lecture IX



Special Report 113
October, 1969

Agricultural Experiment Station
University of Missouri-Columbia

Presented by:

The Brody Lectureship Committee

Dr. R. C. McClure, Sigma Xi representative
Dr. J. E. Savage, Gamma Sigma Delta representative
Dr. Harold D. Johnson, department of dairy husbandry; chairman, Brody Lectureship Committee.

This committee, appointed by Dean Elmer R. Kiehl in September, 1968, with joint sponsorship of the organizations these men represent plans at least one lecture a year.

Loren D. Carlson - Biography

Dr. Loren Daniel Carlson was born in Davenport, Iowa, May 5, 1915. After his education in the Davenport public schools, he attended St. Ambrose College in Davenport, and received a bachelor of science degree in 1937. Dr. Carlson attended the University of Iowa, Iowa City, and received a Ph.D. in zoology in 1941. After a short period as a research associate in the department of zoology, University of Iowa, he was commissioned a 1st Lt. in the U.S. Army and was stationed at the U.S. Army Air Corps Aeromedical Laboratory at Wright Field, Ohio. His work during World War II was related design and testing of oxygen equipment and he finished his active duty career as a Major in charge of the oxygen branch of the Aeromedical Laboratory. He left the service in February, 1946, to become instructor in the department of zoology at the University of Washington. With the formation of the Medical School at the University of Washington, he joined the department of physiology and biophysics in the School of Medicine where he remained until 1960. He was promoted to professor in 1955. During his career at the University of Washington, Dr. Carlson served as an assistant dean from 1948-49 and from 1953-54. Also one year of his tenure was spent as director of general education. In July, 1960, Dr. Carlson was appointed professor and chairman of the department of physiology and biophysics of the newly established College of Medicine at the University of Kentucky. In 1966, Dr. Carlson accepted an appointment as assistant dean and chief of the Division of Sciences Basic to Medicine at the School of Medicine, University of California at Davis. He also is professor and chairman of the department of physiology. Dr. Carlson has served as chairman of the aeromedical panel of the U.S. Air Force, Scientific Advisory Board. He is a member of the medical advisory group for the Office of Manned Space Flight, NASA; the biosciences advisory group for the Office of Space Science and Applications, NASA; and of the Space Science Board of the National Academy of Sciences. He serves on a space technology panel of the Office of Science and Technology. He has served as member and chairman of the physiology training grant committee, National Institutes of Health. Dr. Carlson was awarded the Legion of Merit and the Decoration for Exceptional Civilian Service by the U.S. Air Force. He was awarded a Ph.D. Honoris Causa by the University of Oslo, Norway in 1969. He is a member of the International Academy of Astronautics, the American Physiological Society, American Society of Zoology, Aerospace Medical Association, and the Society for Experimental Biology and Medicine. He is listed in "Who's Who in America." Dr. Carlson is the author of a number of papers dealing with (in the earlier phase of his career) cellular physiology; later with problems of respiratory physiology and the design and development of oxygen equipment and in the metabolic aspects of temperature regulation

during adaptation to cold environments. He was married to Marion Dudley Gross in 1941 and has four children: Eric, Christopher, Allen, and Katherine.

SELECTED PUBLICATIONS (Temperature Regulation and Acclimation)

Human bioclimatology, cold. Chapter 7 in Climate, Health and Disease, Vol. VIII, Physical Medicine Library, New Haven, Conn., Sidney Licht, ed., 1964.

The effects of immersion of the hand in cold water on digital blood flow (with A.C.L. Hsieh and T. Nagasaka). J. Appl. Physiol. 20:61-64, 1965.

Cold (with A.C.L. Hsieh). Chapt. II in Physiology of Survival, O. Edholm and A. L. Bachrach, eds., Academic Press, London 1965.

Role of catecholamines in cold adaption. Pharm. Rev. 18:291-301, 1965.

Responses of cold-and warm-adapted dogs to infused norepinephrine and acute body cooling (with T. Nagasaka). Amer. J. Physiol. 209:227-230, 1965.

Temperature Regulation and Acclimation

(Metabolic and Endocrine Physiology)

Loren D. Carlson
Department of Human Physiology, School of Medicine
University of California, Davis, Calif.

It is a pleasure to accept the honor of being selected to give the Brody Memorial Lecture.* It is a pleasure because of the deep respect I have for Samuel Brody, his institution, his work, and his colleagues. It is also an honor because I join a distinguished line of lecturers in this series. To me, Samuel Brody's book, "Bioenergetics and Growth" [1] is a monument in the literature of environmental physiology. Since my predecessors in this lecture series[2-5] have discussed certain areas of metabolism and temperature regulation in detail, I have chosen today to review the metabolic and endocrine changes which occur during acclimation. I also will discuss and speculate on the shifts in the regulating system which account for these changes. In doing this, I knowingly undertake a rather large task and will borrow the introductory quotation from the first chapter in Samuel Brody's book--"The situation is complicated and its difficulties are enhanced by the impossiblity of saying everything at once." --J. H. Woodger.

I will cover my topic in the following categories. First, a schematic of the temperature regulating system with some detail as to its function. This will serve as the framework on which we can place the observations that have been made. Second, a review of the metabolic changes that occur with exposure to cold and their relationship to the length of time to exposure. Third, the evidence for and the shift in metabolic response to cold from a shivering to a non-shivering thermogenesis; the time courses of these changes; the involvement of the sympathetic nervous system and endocrine glands; and the organs or target tissues. Fourth, a short review of the interesting fact that non-shivering thermogenesis exists in homeothermic animals at birth with some notable exceptions. Fifth, I will discuss the possible metabolic pathways involved in non-shivering thermogenesis. At this point in my lecture, I will change the scene from metabolic heat production to the primary mechanism of heat conservation, peripheral circulation, and introduce the evidence that there is an alteration in the response of the peripheral circulation to cold exposure. This response is evidenced by a change in the blood flow

*Lecture presented at the University of Missouri - Columbia, June 20, 1969.

response to temperature; a change in sensitivity to infused norepinephrine; and a marked difference in the extent to which heat exchanging occurs in the peripheral circulation.

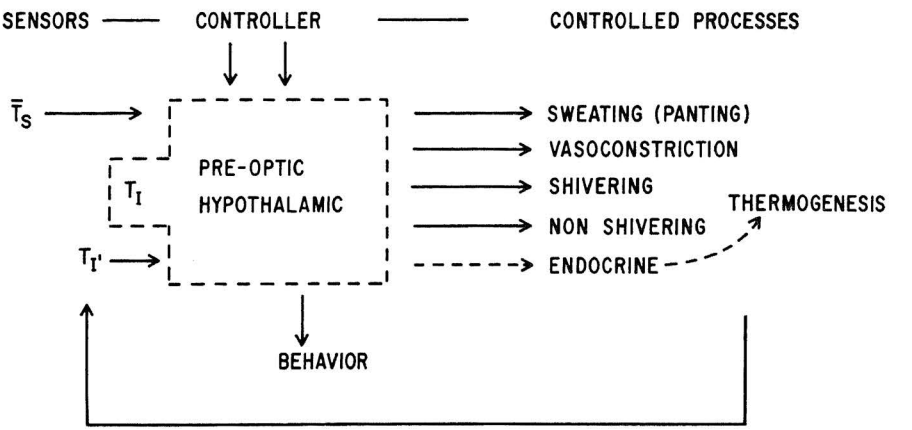


Fig. 1—Diagram of the temperature regulating system.

Figure 1 is the stage for our discussion of the mechanisms involved in a response to cold exposure which imposes a heat load on the homeothermic system. Phrased in control systems terminology, the sensor, a controller, and the control processes are indicated as physiological functions. The elements that are involved in sensing are the skin temperature and an internal temperature (s). One site for internal temperature sensing is in the hypothalamic region. A second may be more peripheral in the core of the body. The control processes (for the purpose of our discussion) are vasoconstriction, a shivering mechanism, and a non-shivering mechanism for the production of heat. The involvement of these two systems are neutral in their direct response but may include the secondary pathways of involvement of certain endocrine glands. The sensing system is given in more detail in Figure 2. Cutaneous receptors for cold are distributed in varying densities on the surface of the skin, relayed by the spinal cord to the thalamic regions and then to the hypothalamic area. The principal outlets for controller pathways are (1) the sympathetic nervous system control of peripheral blood flow (Fig. 3) and of cell metabolism and, (2) the motor system for shivering, shown in more complexity with facilitatory and inhibitory pathways in Fig. 4.

The overall metabolic response may be used to characterize the system's response to cold when referred to environmental temperature or other indices of heat load. We chose to select the mean skin temperature as a significant variable since it is the external sensing site.[6] Continuous exposure of man to cold occasions a shift in the metabolic response

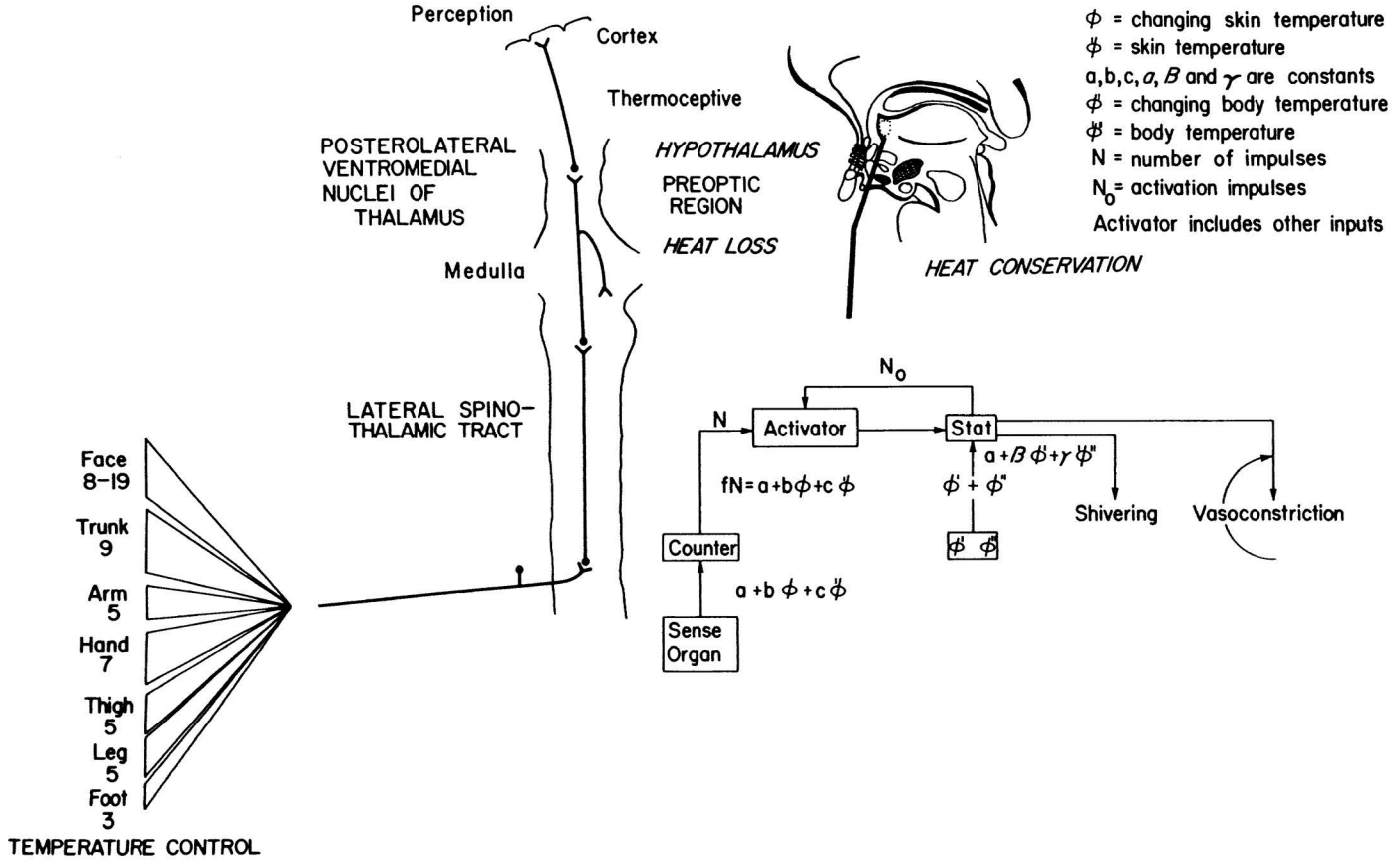


Fig. 2—The sensory pathways for cold detection and a proposal for the mechanism of integration.

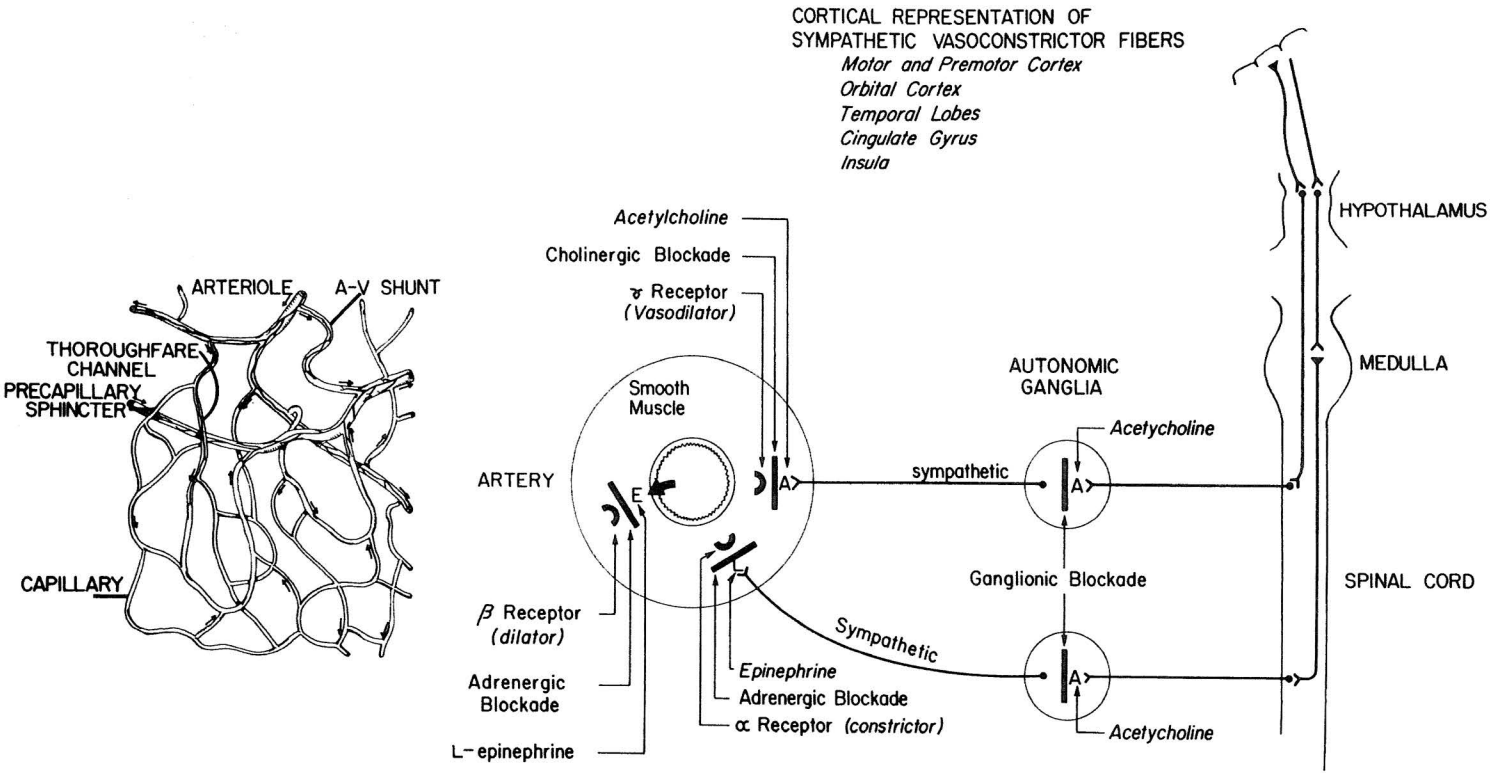


Fig. 3—Pathways for control of the peripheral circulation. Similar pathways to adipose cells would involve primarily beta receptors. (From Green and Kepchar, 1959, Physiol. Rev. *39:* 617-686).

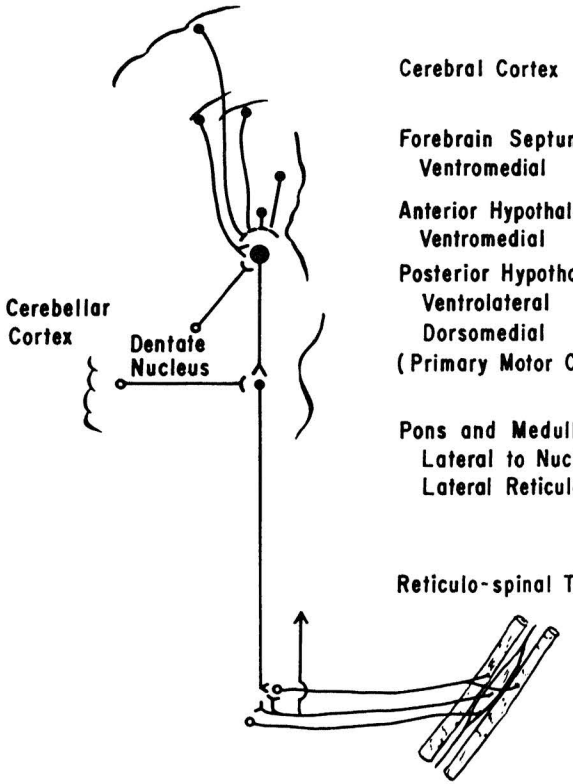


Fig. 4—Motor pathways for shivering. Facilitation shown by Y type endings, and inhibition by T type endings. (Adapted from Hemingway and his collaborators.) (See Hemingway, A. and D.G. Stuart, 1963, Temperature: Its measurement and control in science and industry, Vol. 3, Part 3, Chapt. 36.)

with reference to a given skin temperature (Fig. 5). The data represents two distinct and different experiments. The first is our measurement made on subjects who were exposed to cold in a two-week bivouac in Alaska. [6] At the end of the two-week exposure, the change in metabolism at a given skin temperature is considerably reduced. The second comparison shown is the result of artificially acclimatizing men in a cold room by Davis and co-workers.[7] The similarity is striking.

Many studies have been made on the effects of the exposure of man to cold. Dr. Hsieh and I [8] brought the results of some of these together and plotted them in different ways. (Figs. 6 and 7)

Regression lines of heat production on average skin temperature from overnight experiments are given in Figure 6. The Alaculuf and the Aborigine were able to sleep during the night, but the Eskimo and White apparently could not. Over the range of 33 $^{\circ}$ to 28° skin temperature, the

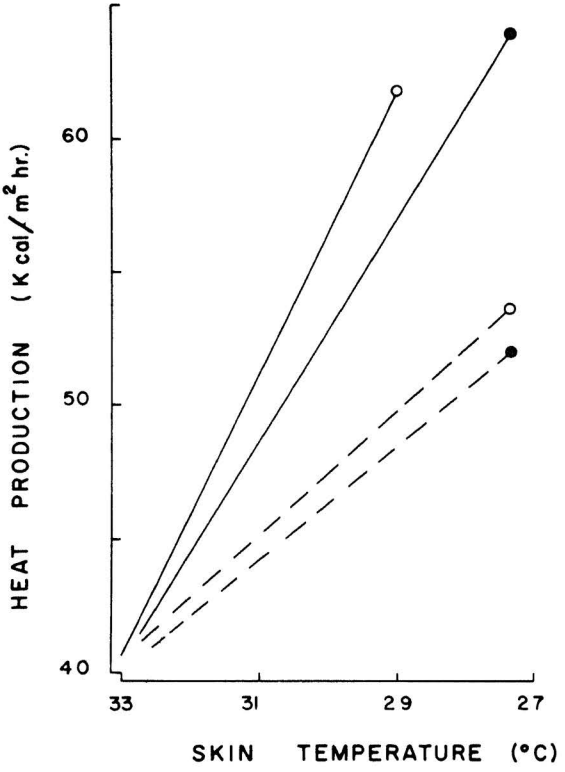


Fig. 5—Heat production as related to mean skin temperature. Solid lines prior to acclimation, broken lines after. Open circles from field study (6), closed circles from laboratory (7).

rise in heat production in response to lowered skin temperature appears to be reduced in Eskimos and absent in the Alaculuf Indians and in Australian Aborigines. There is a considerable difference between the initial metabolic rates of the various groups. However, the response lines of the Eskimos and Alaculufs, who appear to have similar initial metabolic rates, indicate that they have different heat production responses at a similar skin temperature. Skin temperature at which a response will occur in the Alaculuf and the Australian Aborigine and the nature of this response have not been determined. The effect of sleep on temperature has not been defined and is an additional variable in these experiments, as is the known circadian influence on temperature regulation.

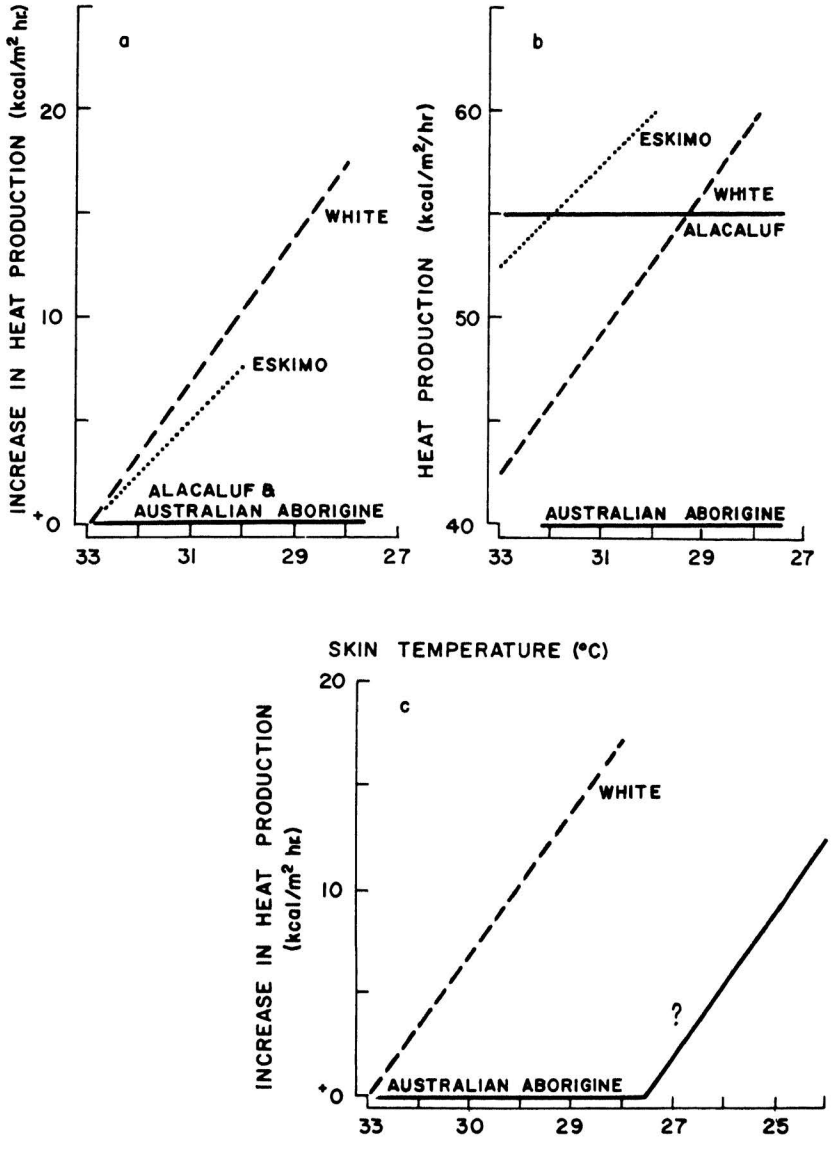


Fig. 6—Data from field studies showing relation of metabolism to skin temperature (from 8). (Expressed as increase in the actual heat production.)

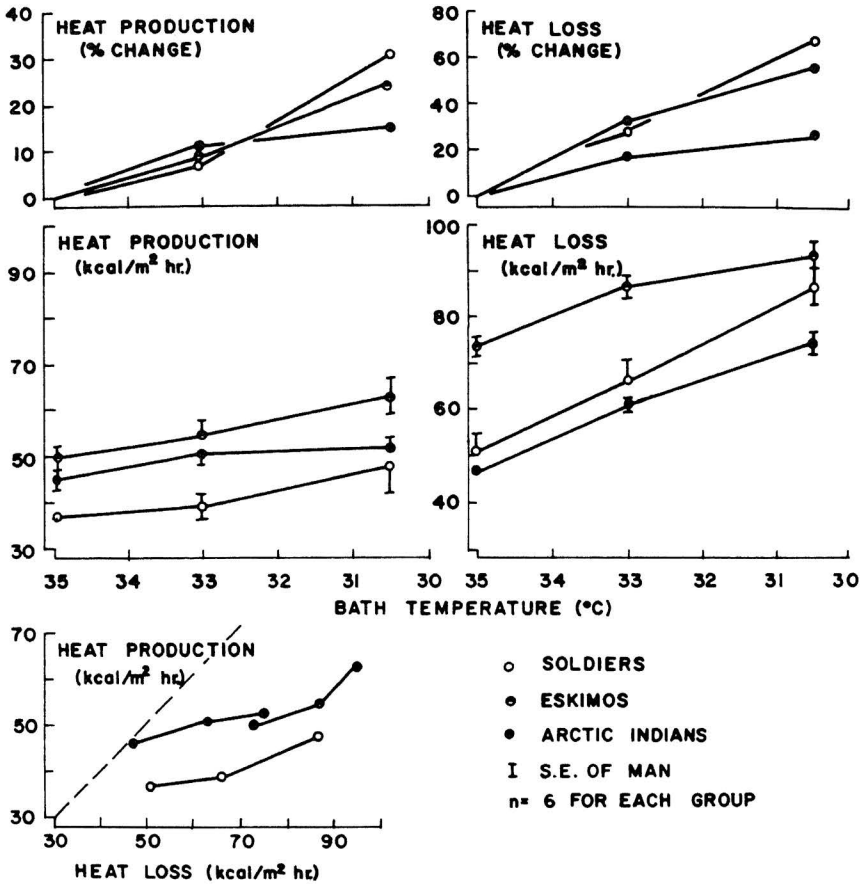


Fig. 7—Bath calorimeter studies indicating the relative change in heat production and heat loss and the actual values in control subjects and Eskimos and Arctic Indians. The plot of heat production against heat loss indicates the intent to which a heat debt is incurred (from 8). Data from Milan.

An exceptional example is the Ama whose shivering response differs greatly from the controls (Fig. 8). We have some evidence in acclimated humans that the extent to which the heat debt may be incurred is also changed with acclimatization.

Heat production and heat loss in a water bath at temperatures of 30.5-35° are shown in Figure 7. When heat production is plotted against skin temperature (taken as bath temperature) the values of change from Caucasian to Eskimos are parallel. However, when these responses are plotted as percentage changes, the Caucasians have greater responses.

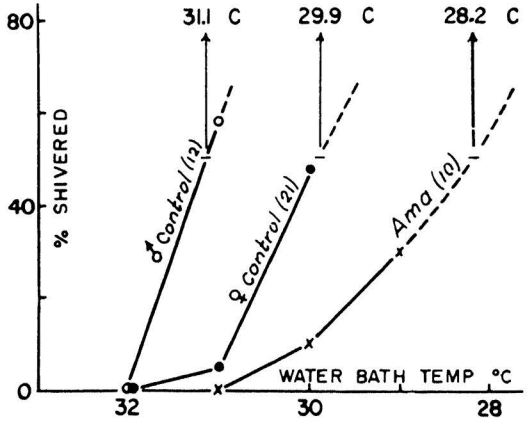


Fig. 8—Incidence of shivering in Ama as compared to control groups. (Figures in parentheses are number of subjects.) (From Hong, S.K., 1963, Fed. Proc. *22:* 831.)

Similar alterations in the relationship between heat loss and skin temperature occur. When heat production is plotted against heat loss, Arctic Indians and Eskimos appear to behave in a similar manner. Caucasians respond at a lower level.

It should be noticed that, in all three groups, heat production is less than heat loss. Thus, the subjects were not in a steady state. These data need to be considered at the end of my discussion with respect to the counter-current heat exchange and the relative amount of shell and core that may participate in the heat loss during cold exposure.

I shall divert briefly to indicate that these methods of assessing change in metabolism as related to skin temperature show there are seasonal differences as well as a circadian rhythm. Not only is the response different in day and night but the thermal conductivity of the body changes. [10]

A generalization from this section could be made. With continued cold exposure, man reacts to any given exposure with less increase in metabolism at any given skin temperature and may provide more heat from storage after cold exposure.

After our field studies in man, which indicated these metabolic shifts as referred to skin temperature, we turned to animal studies in the laboratory to get further information on possible metabolic changes. Sellers, et al., [11] had shown that rats exposed to cold gradually reduced shivering and yet were able to maintain temperature. By curarizing rats to prevent any shivering, Cottle and Carlson [12] and Hsieh and Carlson [13] discovered a metabolic response to cold apparent only in cold exposed animals. The non-shivering thermogenesis thus characterized has received considerable attention.

During Keller's [14] observation on gross shivering, he empha-

sized that cold stimulated non-shivering heat production was just as distinct an entity in dogs as the shivering heat production. He indicated that each has a separate and distinct group of nerve cells and a unique, descending fibre tract in the hypothalamic grey matter and brain stem. DuBois [15] had also found a prevalence of non-shivering thermogenesis in some women studied, and stated that the lack of a significant change in the metabolism of men and some women with a change in environment shows that there must be a chemical regulation which increases metabolism in the core of the body to compensate for the lowering of metabolism in the periphery.

Non-shivering thermogenesis appears to exist in varying degrees in a number of animals and in man. For historical purposes, I would like to review our experiments which characterized non-shivering thermogenesis. Dr. Cottle and I described the marked changes in non-shivering thermogenesis which occur in the rat with continuous exposure to cold. [12] Some of these animals were adrenal demedulated to illustrate the partial involvement between adrenal medulla in the non-shivering response. In attempting to elucidate the mechanism of this response, Dr. Hsieh and I established that the cold induced non-shivering thermogenesis was vulnerable to autonomic blocking agent, hexamethonium. [13] The adrenolytic drug, Piperoxane (an alpha blocker) also prevents cold induced non-shivering thermogenesis. Cold exposed animals are more responsive calorigenically to injected or infused norepinephrine. [13] Jansky and his co-workers [16] have described in an elegant fashion the time course of the metabolic responses of the administration of norepinephrine in the rat with respect to time of exposure and also the temperature of exposure. In Figure 9, the percent increase in the metabolic stimulus from 0.4 milligram

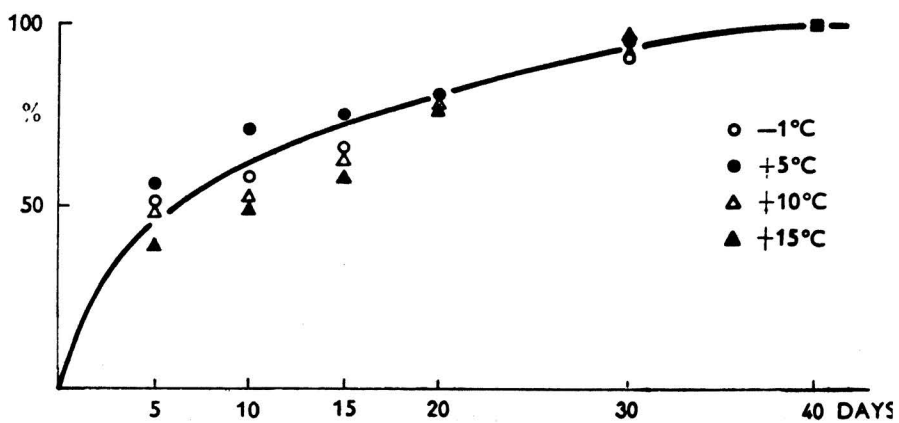


Fig. 9—Percent increase in metabolism after 0.4 milligram norepinephrine per kilogram body weight with time at four temperatures. (From Jansky, et al. [16].)

norepinephrine per kilogram body weight is plotted with time of exposure at four different temperatures. The time course of this response is markedly similar. The decay of the response also has a rather long time course of days following return of animals to a warm environment. It should be noted that the relative effects of temperature in promoting the response are linear, Figure 10. And finally, the maximum of metabolic responses after administration of .2 mg norepinephrine per kg body weight, expressed as a percentage of the resting metabolism, has been determined with varying periods of the day exposure at 5°. The partitioning effect is evident in Figure 11.

Striking as the norepinephrine effect is, there are other endocrines involved in the response to cold exposure. Adrenocortical substances

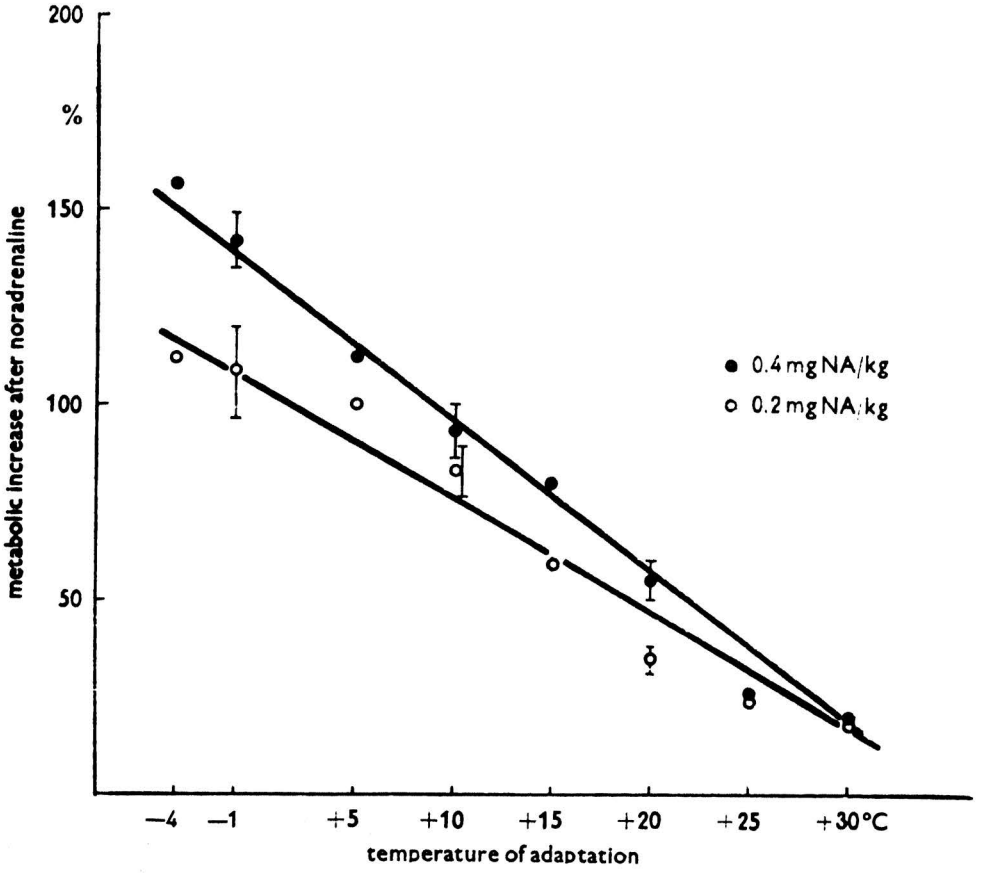


Fig. 10—Metabolic increase after noradrenaline as related to temperature of adaptation (From Jansky, et al. [16].)

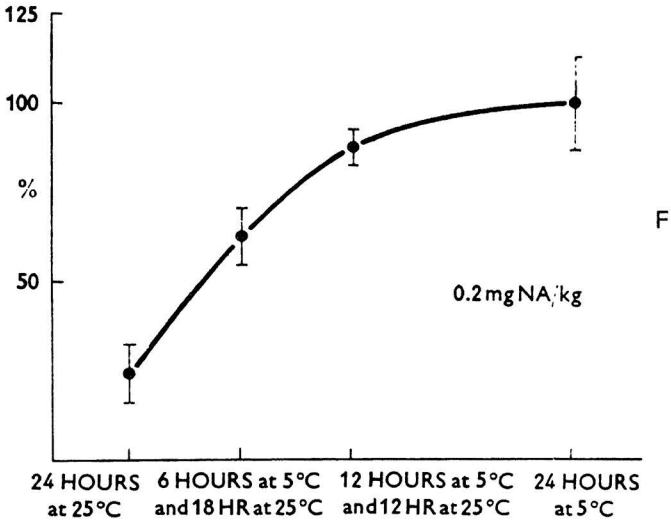


Fig. 11—Partitioning effect of cold exposure. (From Jansky, et al. [16].)

appear only to be related to the initial stress of cold and not required in augmented amounts during cold exposure. Thyroxin requirements, on the other hand, are increased and the turnover rate is more than doubled.[17] However, thyroxin, per se, is not the single factor involved in acclimation since in a thyroid cold acclimated animal, the cold induced thermogenic pattern still appears.

The site of the heat production in non-shivering thermogenesis has been a matter of considerable debate. We suggested the liver or viscera as a possible and teleologically attractive site. Depocas [19] demonstrated that functionally eviscerated animals could respond to cold and infused norepinephrine. Comparative studies of circulation in the whole animal showed that the blood flow increased significantly during cold exposure in muscular organs (heart, diaphragm, skeletal muscles) in warm acclimated rats. In cold acclimated rats, the blood flow to brown fat, white adipose tissue, and the splanchnic area increased significantly and accounted for 65 percent of the increase in blood flow during the cold exposure compared to only 36 percent in the warm acclimated rats (Fig. 12). The cold acclimated animals also have an increased cardiac output during cold exposure. [20]

Before we search for the metabolic pathways that may be involved, we should indicate that thermogenesis is a general phenomenon in the newborn animal. Guinea pigs exposed to cold shortly after birth increase their oxygen uptake with a small amount of shivering as indicated by the electromyogram. The increase in oxygen consumption is blocked by alderlin (a beta blocker) (Bruck and Wunnenberg [21]). This response to cold changes to a predominantly shivering thermogenesis as the animal

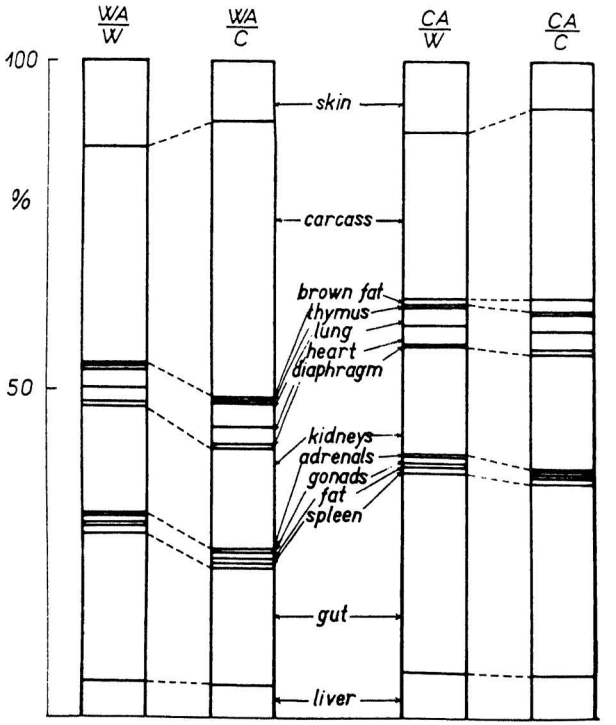


Fig. 12—Fractional distribution of cardiac output in warm acclimated (WA) and cold acclimated (CA) animals exposed to warm (W) and cold (C) environments. (From Jansky and Hart [20].)

grows older. Hagen and Hagen [22] have summarized the data on rats (Fig. 13). Using weight as an index of age, the non-shivering response disappears within a few weeks. This non-shivering response in the newborn has been demonstrated in the rat, guinea pig, cat, and human. At the tissue level, Hagen and Hagen showed that the norepinephrine induced increase in metabolism of adipose tissue was high at birth and decreased--unless the animals were kept cold exposed (Fig. 14). Norepinephrine causes the release of free or non-esterified fatty acids (NEFA) into the blood stream. This effect is altered with cold acclimation. The expected positive correlation between plasma NEFA and a dose of norepinephrine was found in warm acclimated animals (Fig. 15). Plasma NEFA increased with increasing oxygen consumption in warm acclimated animals and decreased in cold acclimated animals (Fig. 16) (Hsieh, et al. [23]).

It would appear that adipose tissue is the primary target for the

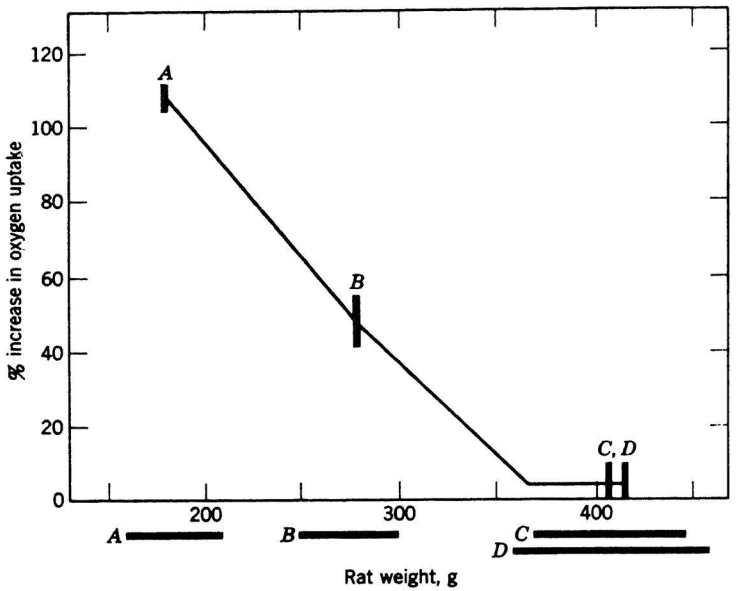


Fig. 13—The effect of age in the calorigenic affect of noradrenaline in the rat *in vivo.* The percent increase in oxygen uptake caused by noradrenaline is plotted against the weight of the rat. The weight of the rat is used as an indication of rat age. (From Hagen and Hagen [22].)

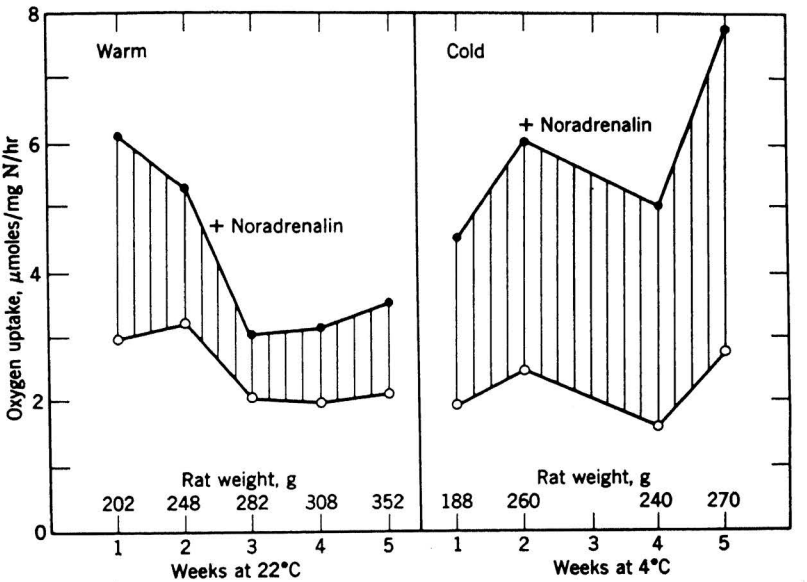


Fig. 14—Stimulation by noradrenaline of oxygen uptake of rat epididymal adipose tissue from warm acclimated and cold acclimated rats. The oxygen uptake in micromoles per milligrams protein nitrogen per hour of paired tissues one incubated with (solid circles) and one without (open circles) noradrenaline 10 micrograms per millimeter is plotted against time. (From Hagen and Hagen [22].)

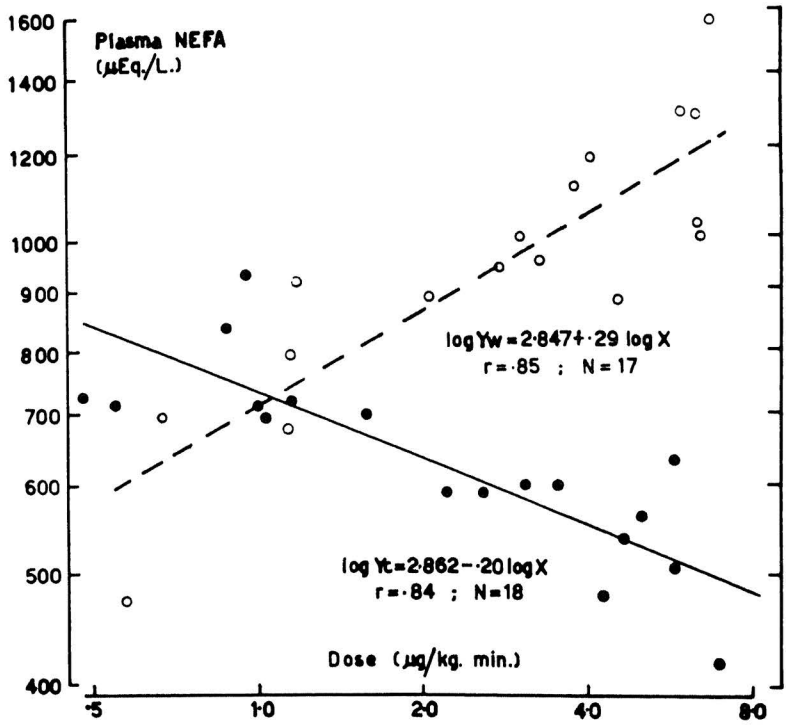


Fig. 15—Plasma NEFA concentrations of cold-adapted rats (closed circles) and warm-adapted rats (open circles) after infusion of norepinephrine for 30 minutes. (From Hsieh, et al. [23].)

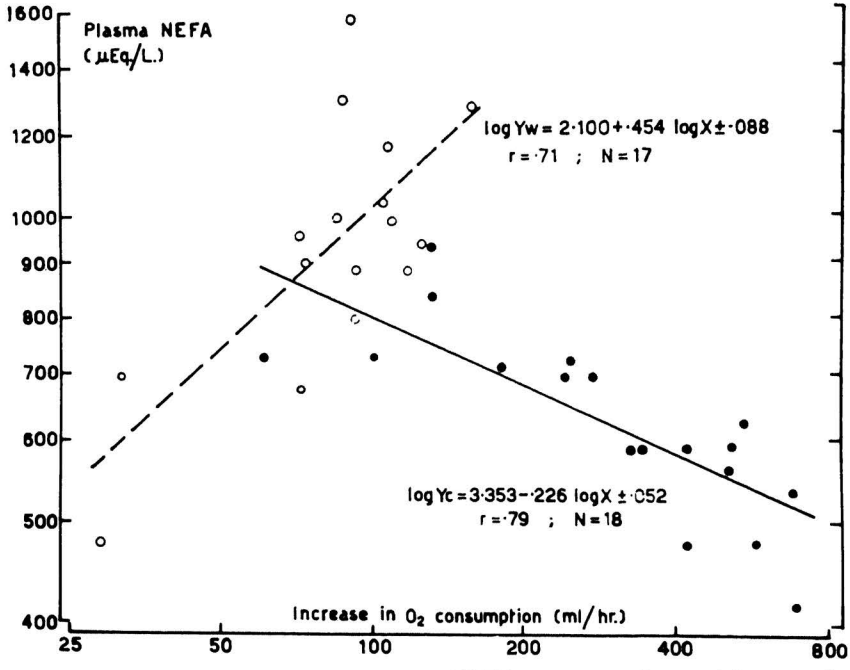


Fig. 16—Relationship between plasma NEFA concentration and increase in oxygen consumption in cold-adapted rats (closed circles) and warm-adapted rats (open circles) after infusion of norepinephrine for 30 minutes.

norepinephrine stimulated thermogenesis. The following remarks of Dr. George F. Cahill [24] in his introduction of Dr. Frank L. Engel at an adipose tissue conference are pertinent. Dr. Cahill refers to the explosive metabolic activity of adipose tissue, and then remarks: "A zoologist friend reminded me that adipose tissue, particularly subcutaneous adipose tissue, does not appear in evolution until the homeotherms. Another friend, an engineer, pointed out that lipid is really not an excellent insulation material. . .

"Placing the knowledge of all three of them together, perhaps one should think of the recycling of triglyceride fatty acids to free fatty acids by lipolysis, activation of the acyl Co-A moiety and esterification with glycerol phosphate as a means of generating heat. Thus, we should think of the subcutaneous adipose tissue not merely as a simple insulating blanket but perhaps as an electric blanket!"

The manner in which a hormone like norepinephrine acts has been schematized by Sutherland and Robison [25] (Fig. 17). Norepinephrine is assumed to act like epinephrine in initiating the cascade effect described by Krebs, et al. [26] (Fig. 18), by way of adenyl cyclase. In fact, insofar as the effects on cyclic AMP are concerned, there appears to be no difference between epinephrine and norepinephrine (Fig. 19). This fact established in vitro is not consistent with the different calorigenic effects of the two catecholamines in the warm-adapted animal nor does it offer an explanation for the change in norepinephrine sensitivity in cold-adapted animals.

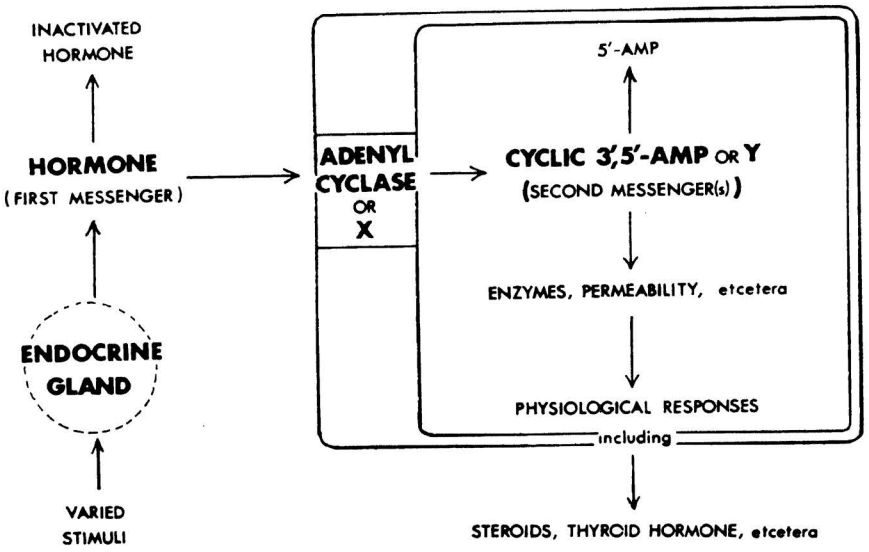


Fig. 17—A schematic representation of the possible action of a hormone such as norepinephrine. (From Sutherland and Robison [25].)

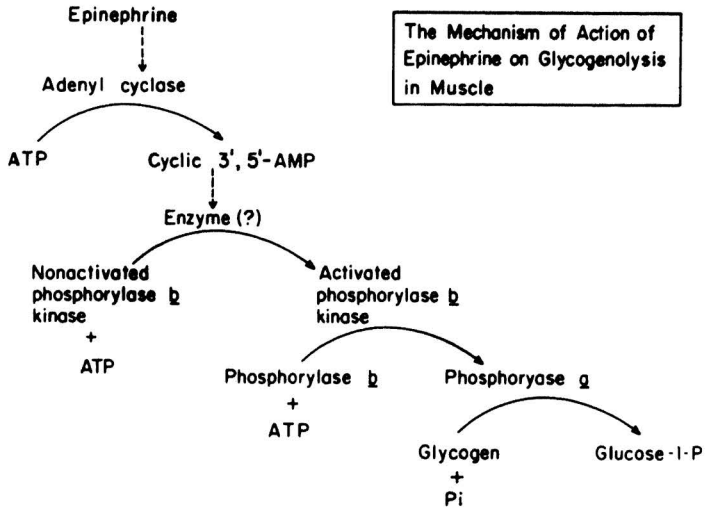


Fig. 18—A possible mechanism of action of epinephrine of glycogenolysis in muscle.

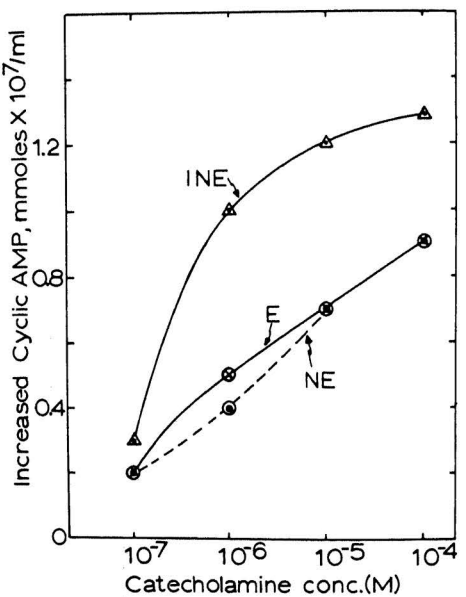


Fig. 19—The effect of various concentrations of the catecholamines on cyclic AMP accumulation by a homogenate of rat epididymal fat. INE, isoproterenal; E, epinephrine and NE, norepinephrine. (From Butcher, R. W. and Sutherland, E. A., 1967, Ann. N.Y. Acad. Sci. 139:849.)

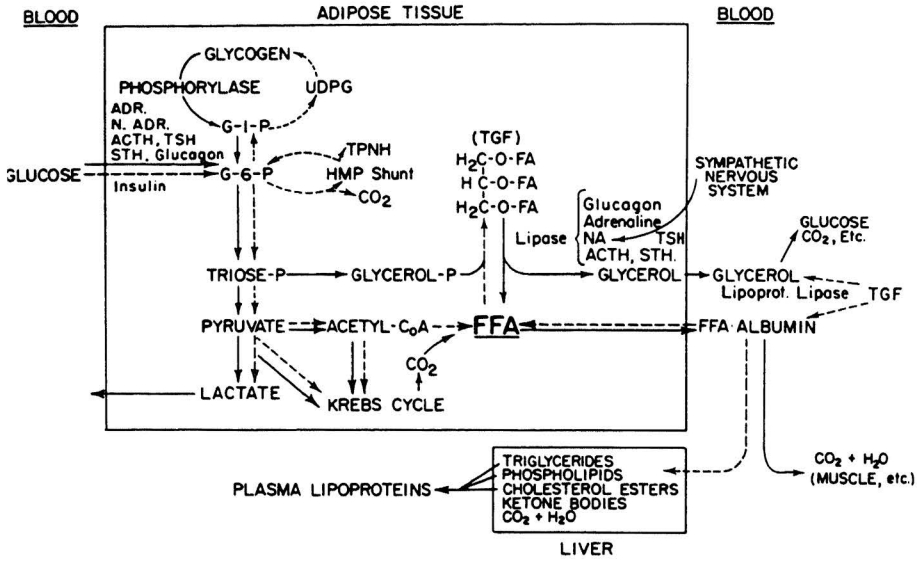
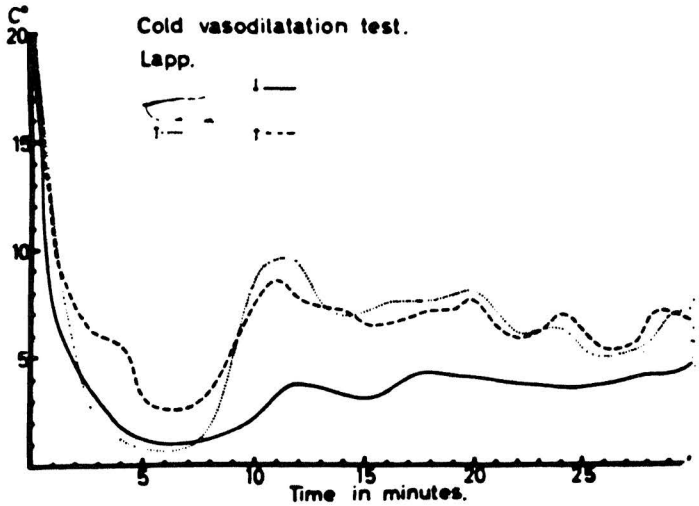
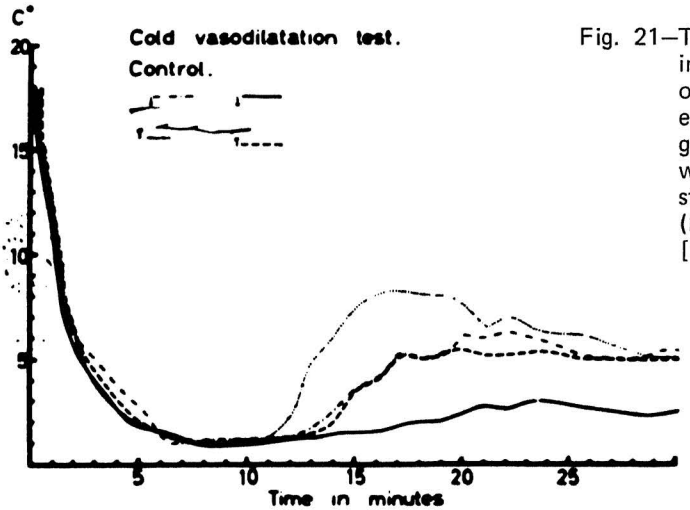


Fig. 20—Metabolic events in adipose tissue based on interpretation of data obtained with *in vitro* techniques. Changes initiated by insulin are represented by dotted arrows and those by lypolytic hormones by solid arrows. No implications of the precise site(s) of action of hormones are intended. (From Sutherland, E. W. and Robison, G. A., 1968, Circulation XXXVII:279.)

The metabolic events in adipose tissue based on interpretation of data obtained with in vitro techniques (Fig. 20), suggests that epinephrine and norepinephrine are rather nonspecific lypolytic enzymes. The assumption would have to be made that this system cycles in order to account for the generation of heat.

I would like to conclude with a brief description of the changes in peripheral circulation observed in the chronic cold exposure. In our initial field studies we made two observations. The first, which I have already mentioned, was the fact that at any given skin temperature, acclimated subjects had a smaller increment in heat production than non-acclimated. Since the avenues of heat loss from the skin were unaltered in the test, the logical deduction was that heat was being supplied from body storage and the idea of the change in ratio of core and shell was introduced. The second observation was that hand temperatures were higher and finger pulse height diminished less during the test cold exposure. These observations have been extended in a number of tests (see Carlson and and Hsieh [8] for summary). A good example is in Figure 21, illustrating the differences observed by Krog, et al. [27], in tests on Lapps and fishermen as compared to control subjects. We studied this further in the





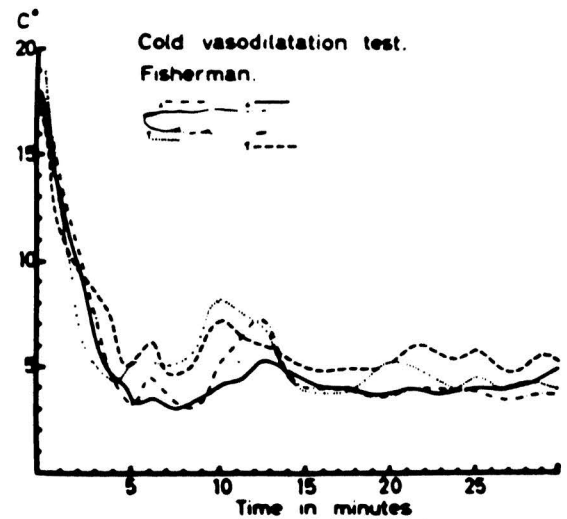


Fig. 21—Temperature curves in time from fingers of one subject from each of the three groups. The fingers were immersed in stirred ice water. (From Krog, et al. [27].)

rabbit ear and have established that the circulatory response in the ear to cold exposure is different and the response to norepinephrine infusion is changed in acclimated animals. Honda's [28] interpretation and analysis of these observations are in Figures 22, 23, and 24. In Figure 22 the model assumes that cooling blood at the surface gives up heat, Q_2. A heat exchanging occurs between artery and vein over a length, L, with a heat value of Q_1. This exchanging mechanism in the transient state cools body tissues if L increases or the exchanging is increased. The ratio of Q_1 to Q_2 is shown in Figure 23. It appears that the cold acclimated rabbit has a considerably greater portion of the body participating in cooling (Fig. 23).

There are intriguing problems here for further study. What mechanisms are involved in providing for the greater heat exchanging and what is the functional status of the sympathetic innervation and norepinephrine metabolism? The interaction of core temperature with the level of peripheral blood flow at a given skin temperature may be a partial explanation.

The mechanisms of adaptation are of interest physiologically because of the time course of development of an altered metabolic and circulatory response to a given cold stimulus. The exploration has made me a jack of all trades and master of none, but is providing a marvelous area in systems physiology for research.

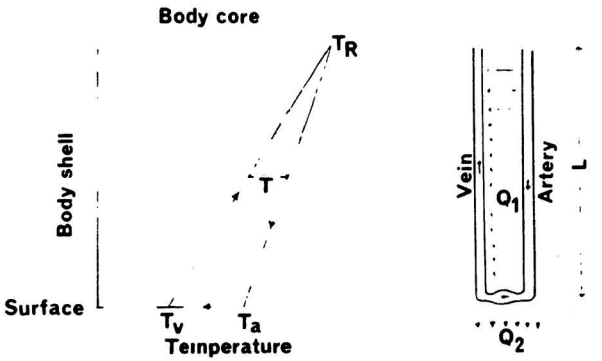


Fig. 22—Schematic illustration of the temperature gradient in a counter current exchanger. (From Honda [28].)

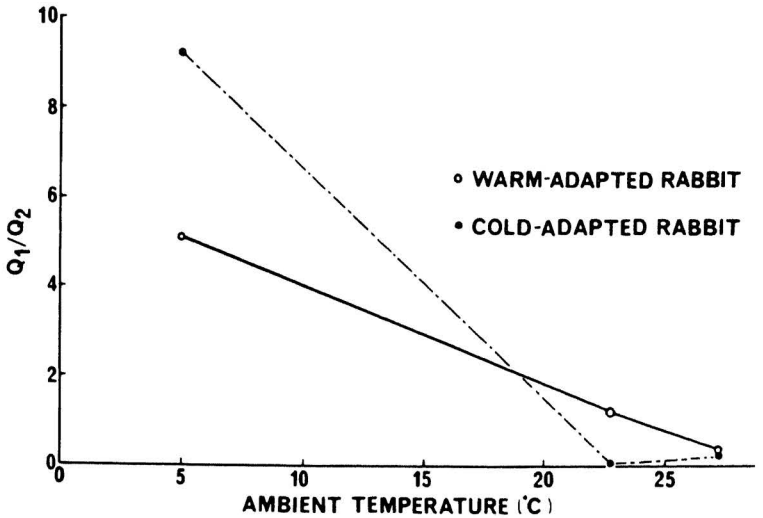


Fig. 23—Relationship between Q_1/Q_2 and room temperature in cold acclimated and warm acclimated rabbits. (From Honda [28].)

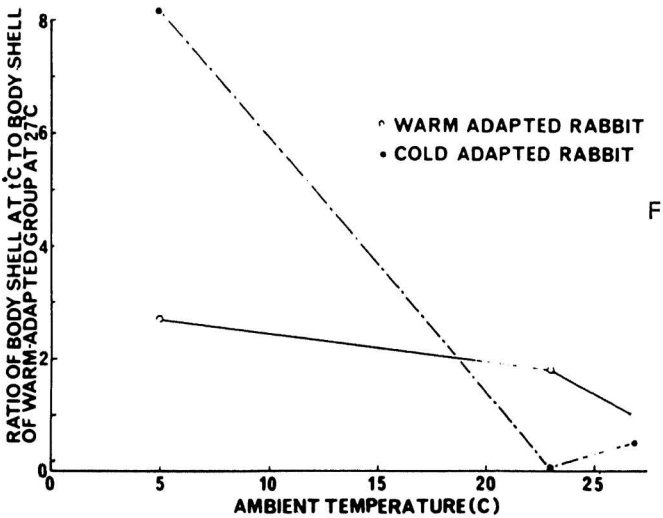


Fig. 24—Relation of body shell thickness to room temperatures. (From Honda [28].)

REFERENCES

1. Brody, S., 1945, Bioenergetics and Growth. New York: Reinhold.
2. Schmidt-Nielsen, K., 1962, Comparative physiology of desert mammals. Univ. of Mo., Ag. Exp. Sta. Spec. Rep. 21.
3. Blaxter, K. L., 1964, Metabolism and metabolic body size: A study with cattle and sheep. Univ. of Mo., Ag. Exp. Sta. Spec. Rep. 43.
4. Prosser, C. L., 1965, Theory of physiological adaptations of poikilotherms to heat and cold. Univ. of Mo., Ag. Exp. Sta. Spec. Rep. 59.
5. Hardy, J. D., 1968, Brain sensors of temperature. Univ. of Mo., Agric. Exp. Sta. Spec. Rep. 103.
6. Carlson, L. D., Young, A. C., Burns, H. L. and Quinton, W. F., 1951, AF Technical Report No. 6247, Wright-Patterson Air Force Base, Dayton, Ohio.
7. Davis, T. R. A., 1961, J. Appl. Physiol. 16: 1011.
8. Carlson, L. D., and Hsieh, A. C. L., Chapt. 2 in The Physiology of Human Survival, Edholm and Bacharach (eds.), 1965. New York: Academic Press.
9. Carlson, L. D., 1963, Temperature: Its Measurement and Control in Science and Industry, Vol. 3, part 3, chapt. 33.
10. Aschoff, J., 1967, Pflug. Arch. 295: 184.
11. Sellers, E. A., Scott, J. W. and Thomas, N., 1954, Am. J. Physiol., 177: 372.
12. Cottle, W. H. and Carlson, L. D., 1954, Am. J. Physiol. 178: 305.
13. Hsieh, A. C. L. and Carlson, L. D., 1954, Am. J. Physiol. 190: 243.
14. Keller, A. D., 1956, in Physiology of Induced Hypothermia, R. D. Dripps (ed.), NAS-NRC Publ. 451, Washington, D. C.
15. DuBois, E. F., Edbaugh, F. G. and Hardy, J. D., 1952, Nutrition 48: 257.
16. Jansky, L., Bartunkova, R., and Zeisberger, E., 1967, Physiologia Bohemoslovaca 16: 366.
17. Cottle, M. and Carlson, L. D., 1956, Endocrinology 59: 1.
18. Hsieh, A. C. L., 1966, Gunma Symposium on Endocrinology, Vol. 3: 239.

20. Jansky, L. and Hart, J. S., 1968, Can. J. Physiol. Pharmacol. 46: 653.

21. Brück, K. and Wunnenberg, B., 1966, Helgolander wiss. Meeresunters 14:514.

22. Hagen, J. H. and Hagen, P. B., 1964, Chapt. 11 in Actions of Hormones on Molecular Processes, Litwack and Kritchevsky (eds.) New York: J. Wiley & Sons.

23. Hsieh, A. C. L., Pun, C. W., Li, K. M. and Ti, K. W., 1966, Fed. Proc. 25: 1205.

24. Cahill, G., 1962, in Adipose Tissue as an Organ, Kinsell, L. W., (ed.). Part III, Springfield: C. C. Thomas.

25. Sutherland, E. A. and Robison, G. A., 1966, Pharm. Rev. 18: 145.

26. Krebs, E. G., DeLange, R. J., Kemp, R. G., and Riley, W. D., 1966, Pharm. Rev. 18: 163.

27. Krog, J., Folkow, B., Fox, R. H., and Anderson, K. L., 1960, J. Appl. Physiol., 15:654.

28. Honda, N., 1965, J. Appl. Physiol. 20:1133.