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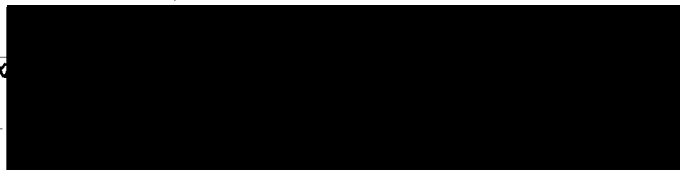
A MODEL OF SHIVERING THERMOGENESIS BASED ON THE CHARACTERISTICS

OF CENTRAL AND PERIPHERAL THERMORECEPTION

by

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ABSTRACT

Five models predicting shivering thermogenesis on the basis of steady state skin and core temperature were evaluated, using the empirical data derived from a cold water immersion study by Morrison, Conn and Hayward . A residual analysis indicated that all models generated substantial errors of prediction. The best overall predictors were expressions suggested by Hayward, Eckerson and Collis , while the prediction equation of Nadel <u>et al</u>. ranked second. Deriving personalized coefficients significantly improved the prediction of all models and a subsequent modification of the standard models, adding temperature derivative terms, further reduced the magnitude of the error. An analysis of the residuals indicated that, peripheral and core temperatures should be weighted according to the characteristics of thermosensitive neural structures in these regions.

A series of cold water immersion trials conducted on five subjects revealed an increase in the thermogenic response with decreasing water temperatures (20°, 15° and 10° C). Shivering thermogenesis was inhibited during cooling and rewarming by inhalation of warm saturated air (40 to 45 C, saturated with water vapour), suggesting a strong central inhibition despite peripheral cold excitation. Observations of lower metabolic heat production at similar levels of core and peripheral temperature, during the warm air breathing immersions, suggested that core cooling rate has a significant influence on the thermogenic

response.

Neurological evidence available in the literature, coupled
with the physiological data obtained from the immersion trials,
provide the foundations for four thermoregulatory models. The
models are based on the response characteristics of
thermosensitive neural structures in the body and derive a
thermogenic response as a result of integration of inhibitory
and excitatory drives from peripheral and core regions. The
gains for the individual neural drives are obtained from a
regression analysis utilizing empirical data. A comparison with
the prediction expressions suggested by Hayward, Eckerson and
Collis and Nadel et al. suggests that the present models are
significantly better predictors. It does not indicate, however,
the need for the inclusion of a dynamic component of the
thermoreceptor responsiveness, as predictions of thermogenesis
are not improved with this consideration. It is suggested, that
the benefits of including dynamic responsiveness of central and
peripheral thermosensitive structures are not apparent due to
the inadequacies of the assumptions incorporated within the
models.

DEDICATION

To Breda, Silva and Nada.

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A. INTRODUCTION

I. Statement of the Problem

The development of empirical methods for monitoring heat loss and heat production mechanisms in animals (reviewed by Benzinger, 1977) in the eighteenth century, aided the search for hypothalamic thermoregulatory centres. It is now accepted (Bligh, 1973; Hensel, 1982) that there exist three main hypothalamic centres involved in the maintenance of normothermia in man: the heat loss centre (Aronsohn and Sachs, 1885), the heat production centre (Isenschmid and Krehl, 1912) and the shivering centre (Hemingway et al., 1954).

The set point concept introduced by Bazett (1949) and later enhanced by Vendrik (1959), attempts to explain the activation of individual centres on the basis of thermosensitivity of central warm and cold sensors. The set point concept has recently been incorporated in the theory of central inhibition of thermogenesis (Benzinger, 1969), suggesting that when the core temperature is displaced from the set point, the ensuing error signal will instigate appropriate thermoregulatory compensating mechanisms. The set point is determined by the response characteristics of central thermosensitive sensors.

Several attempts have been made to derive models predicting shivering thermogenesis due to cold stress, based on the set point concept (Brown and Brengelmann, 1970; Hayward et al., 1977; Nadel et al., 1970; Stolwijk and Hardy, 1966; Timbal et al., 1976a,b). However, each model has been derived from

experimental observations on a specific subject group and may
fail to predict adequately the metabolic heat generation of a
different subject group. A comparison of these models on the
basis of their predictive power has not been conducted.
Comparative evaluations have mostly been made on the basis of
the theoretical concepts underlying the models (Hsu, 1971; Hwang
and Konz, 1977).

An independent evaluation of existing predictive
expressions is difficult, due to the different experimental
paradigms used to obtain physiological data from which the
models are subsequently developed. Due to the lack of such
evaluations, the powers of prediction of models are not known.

Some models are similar conceptually, in that they ignore
the contributions of transient changes in peripheral and core
temperatures to the physiological responses during thermal
exposure. It has been shown experimentally, that such
contributions are significant. Wurster and McCook (1969) have
shown sweating rate to be dependent upon rate of change of skin
temperature and Piantadosi et al. (1981) have concluded that the
metabolic response in hyperbaric environments is affected by
different core cooling rates. Such evidence suggests
consideration of dynamic temperature changes within the body,
when predicting physiological responses to a thermal stress.
There is also neurophysiological evidence justifying the
incorporation of transient temperature components in
thermoregulatory models. Temperature receptors have significant

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dynamic responses to temperature changes (Duclaux and Kenshalo, 1980; Kenshalo and Duclaux, 1977). Although it has been shown that the steady state firing of a cold receptor is proprotional in relative units to oxygen consumption (Hensel, 1976), such a correlation has not been resolved to include the dynamic component of cooling.

To establish a model, predicting physiological responses to a cold stress on the basis of neurological and physiological evidence, requires information on the thermogenic responses to a variety of peripheral and core thermal stimuli. Most thermoregulatory studies on humans incorporate complex experimental protocols, but the data are often reported as averaged data of the subjects, thus obscuring transient responses which would otherwise be evident on individual subject observations.

Ideally, a thermoregulatory model should simulate the response characteristics of thermosensitive neural structures involved in the thermoregulatory control system. The prediction of physiological responses should be established on the basis of excitatory and inhibitory interactions of these neural structures in various regions of the body. When incorporating the set point concept, it should be realized that the change in firing rate of cold and warm receptors, due to cooling and rewarming, follows the bell shaped relationship initially observed by Zotterman (1953).

To date, there have not been many attempts to combine the physiological and neurological mechanisms of thermoregulation in thermoregulatory modelling. This has partly been due to insufficient knowledge on the mode of interaction of various inhibitory and excitatory thermoregulatory drives at the extrahypothalamic and hypothalamic levels.

II. Statement of the Purpose

The aim of the present study was to evaluate the ability of several models to predict shivering thermogenesis during cold water immersion and rewarming (Brown and Brengelmann, 1970; Hayward et al., 1977; Nadel et al., 1970; Stolwijk and Hardy, 1966; Timbal et al., 1976a) with experimental data obtained from a study by Morrison et al. (1982). It was hypothesized, that the errors of prediction would be minimized, if the standard models were modified to account for peripheral and core cooling rates.

A series of cold water immersion and rewarming trials were designed to establish the contributions to shivering thermogenesis of dynamic temperature changes imposed on peripheral and core regions in humans. It was envisaged, that the empirical evidence would extend present knowledge of the effects of static peripheral temperatures (10°, 15° and 20° C) at various core cooling rates on the metabolic heat production in man.

Finally, the study proposed to combine the observations on the physiological responses of man to cold water immersion, with neurological data on response characteristics of thermosensitive neural structures involved in thermoregulation, to develop a model predicting shivering thermogenesis.

III. The Scope of the Study

The study consists of four major sections:

Section B : The first section offers a review of

thermoregulation with particular reference to cold exposure.

The development of thermoregulatory physiology is discussed

from a historical point of view. This is followed by a

review of neurophysiology of thermoregulation. The

complexity of the neural network controlling thermal

homeostasis warranted separate discussions on temperature

transducers (thermoreceptors), the extrahypothalamic and

hypothalamic thermoregulatory control loops and the

interaction of these systems to maintain normothermia. The

cardiovascular, muscular and metabolic adjustments,

resulting from excitatory and inhibitory interactions of the

neural systems are discussed in a review of physiological

studies on cold exposure. The review is concluded with an

overview of various attempts to model the thermoregulatory

system in humans.

Section C : Predictive equations of thermogenesis are evaluated

using data selected from the literature (Morrison et al.,

1982), to determine their power of prediction. These

stimulus-response relationships are modified to minimize the

error of prediction. Dynamic terms are then added to the

expressions to determine their effectiveness in reducing the

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residual error.

Section D : The thermogenic responses of five subjects were
evaluated, while undergoing a series of immersion trials.
The immersion trials consisted of immersion in three
different temperatures of water, with and without donation
of respiratory heat to the core. Therefore, at each water
temperature, two different core temperature transients were
imposed on the subjects. Thermoregulatory responses to these
temperature stimuli were evaluated on the basis of metabolic
and cardiovascular adjustments.

Section E : A thermoregulatory stimulus-response model was
derived, incorporating physiological evidence of section D
and neurological observations reported in the literature.
The model is based on the theory of superposition, thereby
allowing the inclusion of a response time function (or
transient). This allows shivering thermogenesis to be
expressed in terms of steady state and dynamic temperature
changes of the surface and core areas of the human body. The
model was evaluated with the data obtained in section D.

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IV. The Rationale for the Study

Although the theory of central inhibition of thermogenesis
is gaining wide acceptance, there is insufficient experimental
evidence supporting its role in humans. Benzinger's results on
one subject (presented in a review in 1969) have not been
reproduced successfully (Craig and Dvorak, 1966) and there
exists a controversy as to the characteristics of the metabolic
response at lower skin and core temperatures. In general, there
has been a disregard for the contributions of dynamic
temperature changes at skin and core regions on the metabolic
response.

Various mathematical expressions exist, relating metabolic
heat production to peripheral and core temperatures. These
expressions have been derived from averaged data of a wide
variety of individuals, and their powers of prediction on
individual subject data are not known.

The predicted metabolic heat production of the expressions
suggested by Hayward et al. (1977) and Stolwijk and Hardy (1966)
are used by more complex thermoregulatory models developed by
Wissler (1970) and Stolwijk and Hardy (1966) respectively, to
evaluate heat exchange between different tissues in the body and
the overall heat loss from the body to the environment. Any
errors generated in estimation of heat generation by the
predictive expressions, may lead to substantial inaccuracies in

the prediction of overall heat exchange by the latter models.

V. Presentation of the Study

The thesis is organized as a collection of separate studies conducted in the area of thermoregulatory modelling and physiology. Although the sections are separate entities, the conclusions and data derived from one section are the foundations and therefore an integral part of other sections.

Several peripheral observations have been made in the course of the study. So as not to dilute the major points being discussed in sections B, C, D and E, these observations are presented as short reports in appropriate Appendices .

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B. THERMOREGULATION IN A COLD ENVIRONMENT. A REVIEW.

I. Introduction

Modern theories on the regulation of internal body temperature began to evolve towards the end of the 18th century. Up to the time of Lavoisier's discovery of the oxidative theory of combustion in 1777, philosophers and scientists placed the main emphasis on explaining the existence of temperatures greater than ambient temperature within the body, rather than how this temperature was controlled or regulated. The latter subject has been of prime interest to thermal physiologists for the last two centuries.

The earliest scholarly discussions on body temperature date back to the era of the Greek philosophers, most notable Plato (Cornford, 1957), Aristotle (Peck, 1943) and Galen (Brock, 1947). Plato conceived the internal heat in humans and animals to be derived from a 'vital fire' within the heart, which Aristotle emphasized needed fuel for maintenance and a method of cooling. Violent death, he reasoned, was due to rapid extinction, whereas natural death was due to exhaustion of the 'internal flame'. Much later, in the 2nd century A.D, Galen reviewed the work of his predecessors and elaborated, that the fatty parts of the body act as fuels for our 'vital flame', analogous to oil being burnt by a flame in an oil lamp. Galen identified a crucial point when he suggested that respiration was somehow involved in supplying our 'vital fire' with a

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substance pertinent to its existence. If respiration were to cease he postulated, the 'internal flame' would be extinguished.

It is not surprising that the combined theories of Aristotle and Galen on the internal body temperature formed one of the longest lived medical and biological doctrines, as conclusions drawn from analogies did not require additional proof.

It was not until the 17th and 18th century that scientists began to adopt different perspectives on the issue of body temperature and by doing so, to undermine the Aristotle - Galen theory. An excellent account of the development of scientific thought on this topic has been presented by Mendelsohn (1960).

Once an explanation had been formulated for the existence of body temperature, through the consumption of oxygen and production of carbon dioxide (Lavoisier 1777 a,b) there existed growing interest in the theory of regulation of body temperature. Seguin and Lavoisier (1785) observed that exposing a human body to low ambient temperatures increased the amount of heat generated, quantified by the increased consumption of oxygen. They observed that individuals consumed 10% more 'vital air', when exposed to environments of $9.6^{\circ}C$ as opposed to $20.8^{\circ}C$ (original values were 12 and 26 degrees respectively, of a thermometer whose scale between the freezing and boiling points of water was divided into 80 degrees). Prior to the observations of Lavoisier and Seguin of the thermogenic response of man in a cold environment, Franklin (1758) reported his observations on

the evaporative heat loss from the body and linked this

phenomena to the maintenance of internal body temperature.

From the 19th century onwards, the science of human thermal

homeostasis proceeded in several directions. The progress in

each field is pertinent to the overall understanding of human

thermal regulation and in the pursuit of clarity, will be dealt

with in separate sections.

II. Neurophysiological Thermoregulation

Historically, neurological investigations of the thermoregulatory system can be assigned to the following categories:

- the search for structures in the central nervous system associated with the maintenance of body temperature within narrow limits.
- theory of peripheral sensory functions; in particular the conveying of thermal information from the periphery and core to the structures in the central nervous system (CNS)
- integration of thermal information.

This review outlines present knowledge on the involvement of certain neural structures in mammalian thermoregulation (thermoreceptors, hypothalamic and extrahypothalamic thermoregulatory centers). The review of neurophysiological thermoregulation is concluded with a discussion on how these neural structures interact in maintaining normothermia.

Temperature Receptors

The transmission of information about the environment to the brain involves four major receptors, situated in the skin. These receptors are classified as cold, warm, pain and pressure receptors. The former two are concerned solely with the transduction of thermal stimuli. If the temperature perceived is either below or above the range of cold and warm receptors respectively, pain receptors (nociceptors) are triggered and the sensation perceived will be pain (Guyton, 1976; Mountcastle, 1980). Cold and warm receptors are defined as receptors which increase their frequency of discharging neural impulses when the temperature is either lowered or raised about the normal skin temperature respectively. The static response of both receptors in cats, first outlined by Zotterman (1953), reveals that cold receptors also fire within a short interval beyond the warm receptor region, at temperatures above 45°C (Fig. 2.1). Also , there seems to exist a second maximum frequency of discharge for cold receptors, at temperatures between 10°C and 15°C, as indicated in Fig. 2.1. The second peak was not observed in the studies of Hensel and Boman (1960), Iggo (1969) and Hensel (1974). Since Zotterman investigated much lower temperatures in comparison, he may have been recording from cold sensitive pain fibres, which according to Guyton (1976) are stimulated at temperatures below 15°C and approach a maximum firing rate at approximately 8°C.

Fig. 2.1 : Static firing response of a single cold fibre (closed circles) and a single warm fibre (open circles). Adapted from Zotterman (1953).

Temperature (°C)

Impulses / sec.

20b
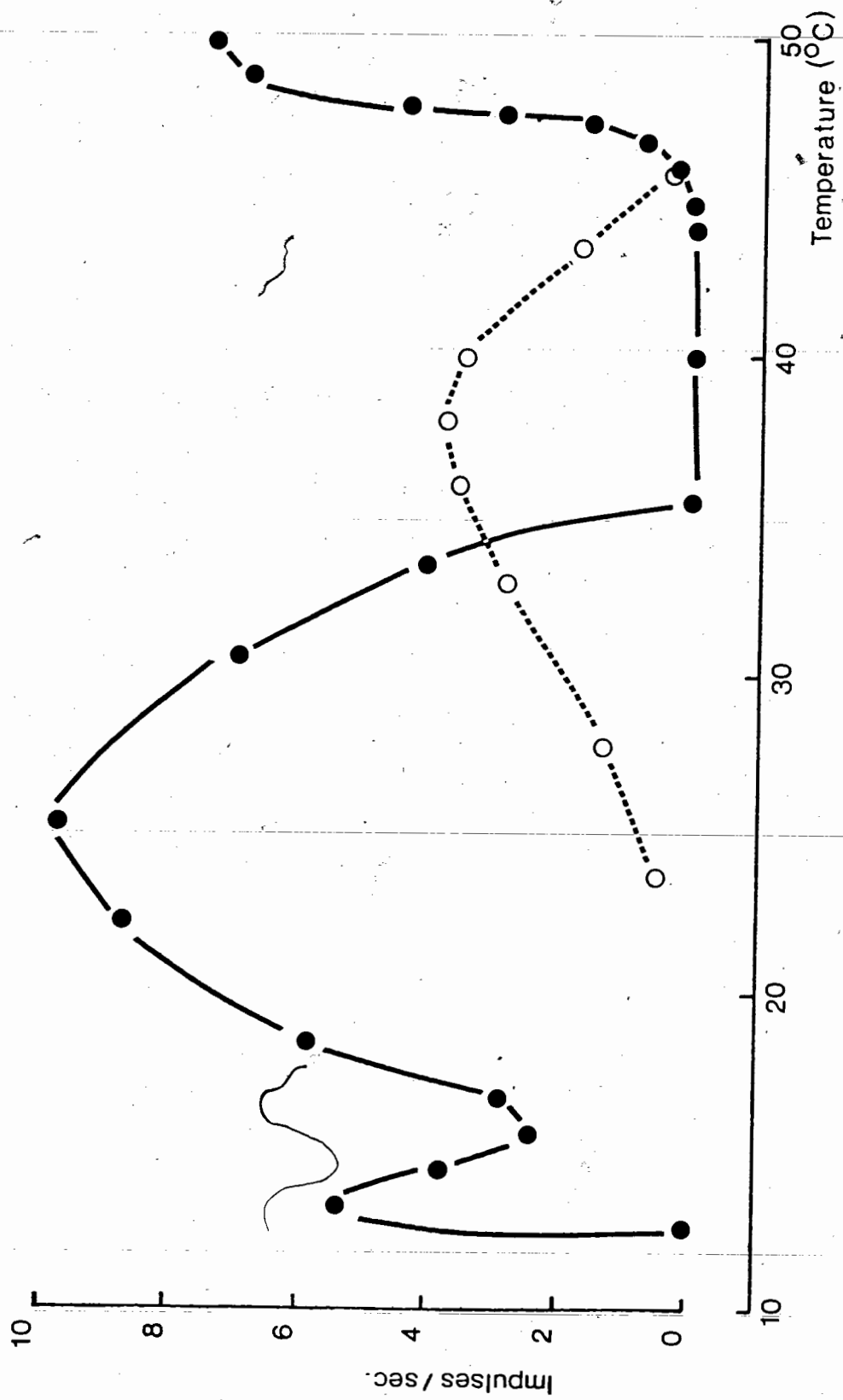
The relationship between static firing rate and temperature of thermoreceptors, as shown in Fig. 2.1, is constructed from average measurements obtained in animal studies; a similar response has been confirmed in humans (Hensel and Boman, 1960). In practice, the maximum frequency of discharge as well as the temperature range of excitation varies for individual fibres. Peak firing rates have been observed in the range of 18° to 34^OC for cold receptors (Hensel, 1974; Kenshalo and Duclaux, 1977) and between 37.5^O and 40^OC for warm receptors (Zotterman, 1953; Duclaux and Kenshalo, 1980).

Zotterman has shown that a step change in temperature will elicit a dynamic response from both types of receptors. As can be seen from Fig. 2.2, there is an initial overshoot and undershoot in the discharge frequency of warm and cold fibres respectively, when increasing the temperature from an arbitrary temperature T1 to T2. Conversely, a step decrease in temperature will cause an overshoot in the cold receptor firing rate and undershoot in warm receptor discharge frequency. In both instances the frequency of firing approaches exponentially a steady-state value, after the initial dynamic phase. The initial dynamic response of thermoreceptors to a step change in temperature has been shown to be dependent on the magnitude of the change in temperature and the thermosensitivity of the receptors (Hensel, 1982; Kenshalo and Duclaux, 1979).

It is evident from Fig. 2.1, that the bell shaped static frequency response of both thermoreceptors makes it impossible

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Fig. 2.2 : Generalized dynamic firing response of a single cold and warm fibre to a rapid temperature change. From Hensel (1982).

STATIC   DYNAMIC

IMPULSE FREQUENCY

WARM RECEPTOR   WARM RECEPTOR

T_1 T_2

COLD RECEPTOR   COLD RECEPTOR

T_1 T_2

TEMPERATURE

TEMP.

T_1 T_2 T_1

TIME

22b
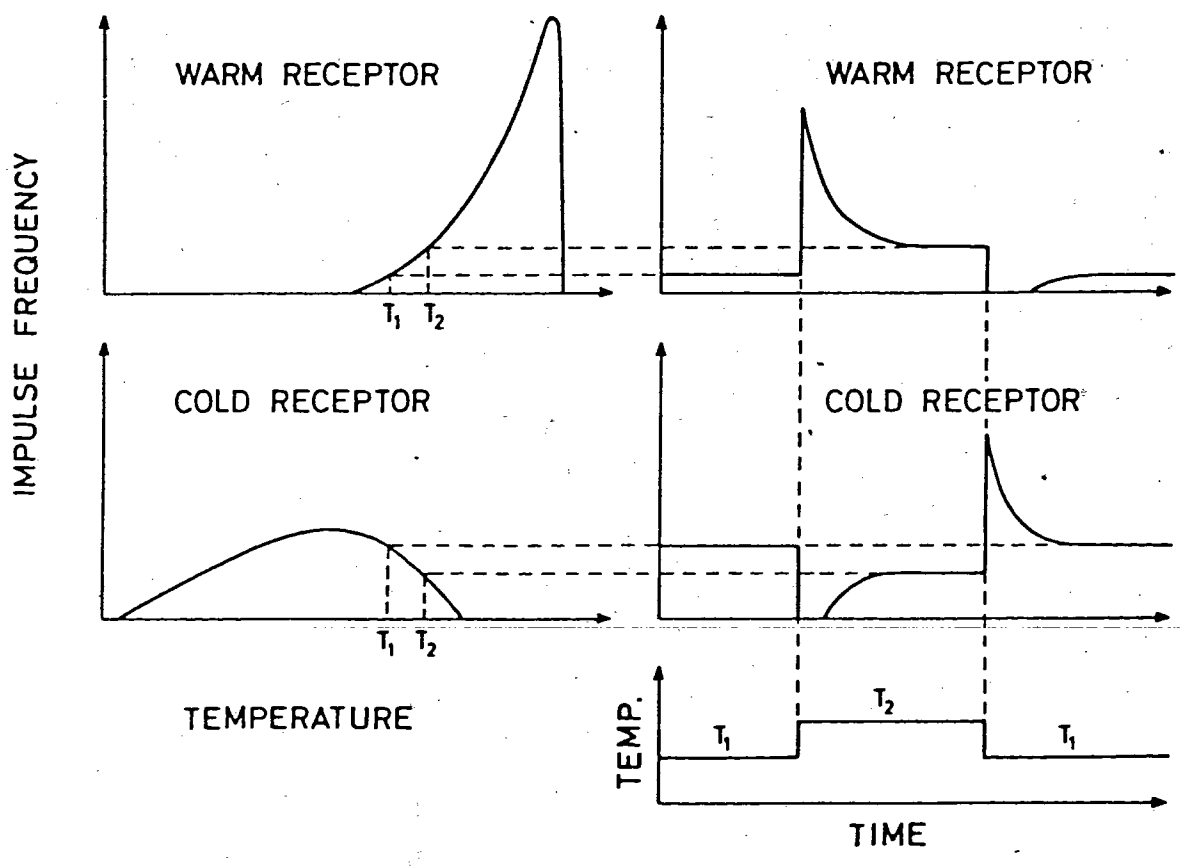
to estimate the temperature from just the knowledge of the impulse frequency of an individual fibre. Two possible explanations of how thermoregulatory centers distinguish temperatures from cutaneous receptor discharge, have been offered. From his work on cutaneous thermoreceptors in primates, Iggo (1969) observed that not only did thermal stimuli influence the frequency of impulse discharge, but they also influenced the coding of the impulses into bursts. Hence, as seen from Fig. 2.3, information on the frequency of impulses coupled with the number of impulses per burst, enables accurate estimation of thermal stimulus. The second possible method of obtaining unequivocal information at any temperature, is from information on the static discharge from both cold and warm receptors (Hensel, 1974).

Generally, findings of neural function of thermoreceptors obtained from experiments on primates (Iggo, 1969) and cats (Hensel, 1974), correspond to the results obtained with human receptors (Hensel and Boman, 1960). Hensel and Boman (1960) also noted that 70% of the human cutaneous mechanoreceptors responded to warming.

The perception of temperature from core areas of the body has been an issue of dispute among thermoregulatory physiologists, which as yet has not been completely resolved. Although core temperature is usually measured rectally, the failure to explain thermal responses on the basis of skin and rectal temperature prompted Benzinger (1969) to pronounce rectal

Fig. 2.3 : Effect of steady state temperature on the discharge
   of impulses in bursts, from a cold receptor.
   a.   The mean frequency (reciprocal of interspike interval)
        and the number of bursts (cycles) per second are least
        at low temperatures, show a maximum at an intermediate
        temperature and decline slightly at still a higher
        temperature. Outside the limits of 20° and 35°C, the
        groups of impulses were absent.
   b.   The number of impulses in a burst and the ratio of the
        mean frequency within a burst to the number of bursts
        (cycles) per second also fell progressively, from low to
        high temperatures.
   Adapted from Iggo (1963).
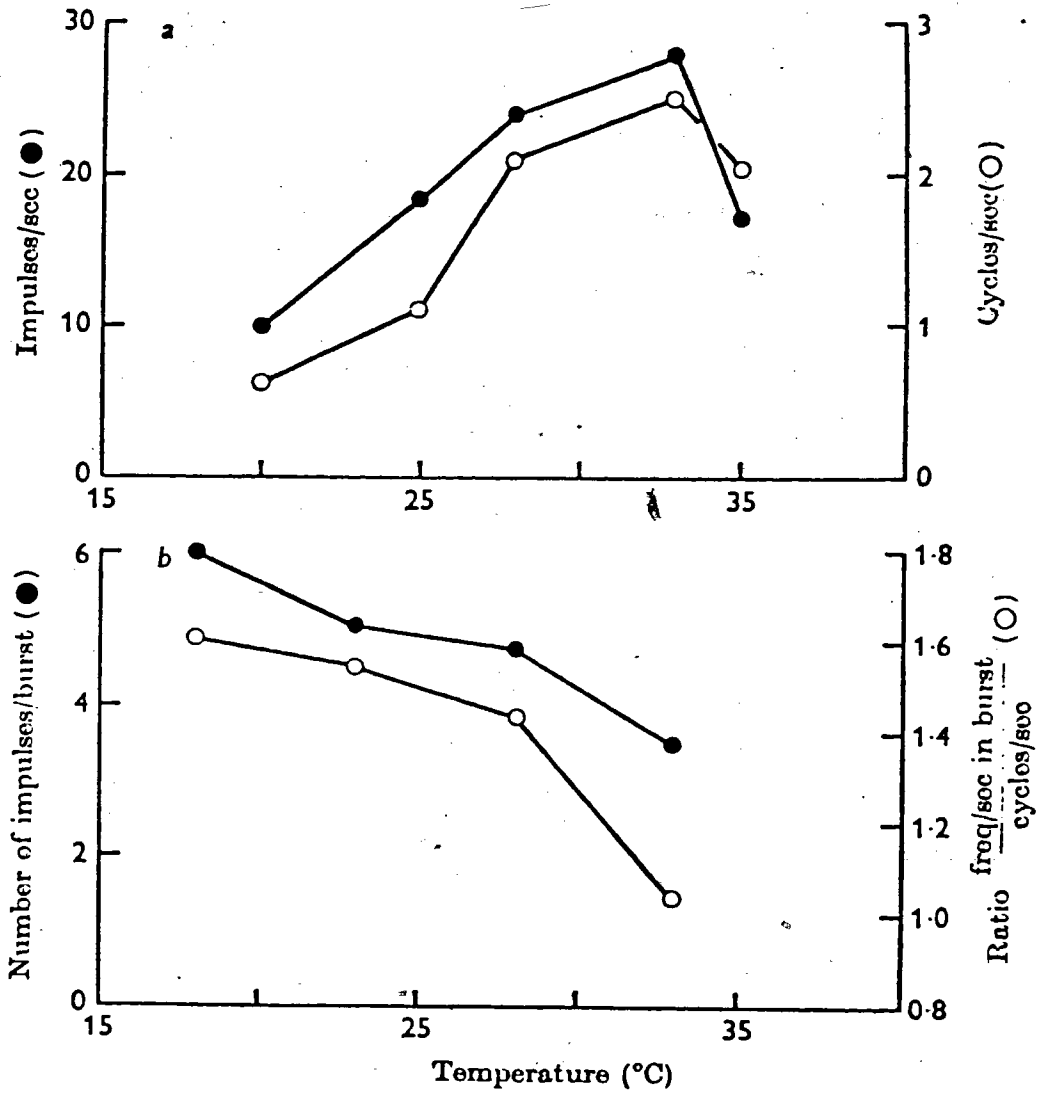
temperature as a useless measure, there being no scientific evidence to support the existence of core thermoreceptors. Instead, models incorporated intramuscular temperature as core temperature (Stolwijk and Hardy, 1966).

The acceptance of core temperature as a significant determinant in the regulation of body temperature, came with the findings of Rawson and Quick (1971, 1972) who induced thermoregulatory responses of shivering and panting in sheep at neutral environments, by intra-ruminal cooling and intra-abdominal heating respectively. Intra-abdominal heating of sheep in cold environments was also found to suppress shivering thermogenesis. Their results point to the existence of thermoreceptors innervated by splanchnic nerves (afferent pathway) in the walls of the rumen, intestine and mesentric veins. Recently, Minut-Sorokhtina and Glebova (1974) have observed static and dynamic (peak frequency of approximately 40 impulses per second for a temperature drop from $30^{\circ}C$ to $17^{\circ}C$) responses of 'touch-cold' receptors of subcutaneous veins and cutaneous vessels similar to those reported for skin thermoreceptors. There was also evident grouping of impulses into bursts for various temperature levels.

Despite the voluminous amount of data on the response characteristics of thermoreceptors, the mechanism by which thermal energy is transduced into neural impulses, that travel via afferent pathways to the CNS, remains unresolved (Sperelakis ,1970) . A unique aspect of thermoreceptors, is

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their ability to transduce a static temperature stimulus. This phenomenon gave rise to several theories, classified by Bligh (1973) as :

1. gradient theory

2. thermocouple theory

3. temperature-dependent endogenous activity theory

Neither the gradient theory, proposing that sensitivity at a constant temperature is due to a heat flux generated by a temperature gradient in the skin, nor the thermocouple theory, suggesting the importance of the direction of the temperature gradient, proved to be valid. The temperature dependent endogenous activity theory suggests that the temperature sensors are triggered by thermal energy into releasing a proportionate amount of energy stored in the internal structure of the sensor. The nature of this chemical energy is yet to be determined. Bligh (1973) suggests that the tonic discharge of a receptor, resulting from depolarization and repolarization of the membrane, is due to an internal oscillatory mechanism.

Although there still exists some uncertainty surrounding the mechanism of thermal transduction, several theoretical models have been proposed (Sperelakis, 1970; Zerbst and Ditterberner, 1970). Much more successful have been attempts at modelling the thermal responsiveness of cold and warm receptors.

On the basis of empirical data, Kenshalo et al. (1976) derived a mathematical model, describing the static and dynamic characteristics of cold receptors.

Hypothalamic Thermoregulatory Centres

Heat Loss and Heat Production Centres

A milestone in the advancement of thermoregulatory theory was the discovery of the heat loss centre in the hypothalamus by Aronsohn and Sachs (1885; earlier hinted at by Tschetschichin, 1866 and Ott, 1884, 1887, 1889), who demonstrated that a lesion made close to the midline, near the anterior portion of the third ventricle, caused the rectal temperature in a dog to rise in conjunction with an increase in metabolic rate. The validity of these findings was at first questioned on the grounds of the experimental procedure used; electrical stimulation with a 'piqure needle' was not a standard practise. The arguments that ensued are well documented by Bligh (1973) and Benzinger (1976).

Before the skepticism shrouding the evidence of Aronsohn and Sachs over the findings of a heat loss centre in the pre-optic anterior hypothalamus could be disproved, the discovery of the second thermoregulatory centre was reported by Isenschmid and Krehl (1912). Using standard transection techniques, they found that the ability of dogs to thermoregulate was abolished by the destruction of the

telencephalon and mesencephalon. The scientific community was undecided at the time, over which heat centre to accept or whether there were actually two separate heat centres in the pre-optic hypothalamus.

Meyer (1913) proposed the existence of a coupling between the two centres. His suggestion of reciprocal inhibition of the thermogenic (pre-optic posterior hypothalamus, POPH) centres was later reinforced by Ranson and Ingram (1935), who found that rhesus monkeys with lesions in the rostral portion of the anterior hypothalamus, were unable to respond to heat stress, while lesions made in the posterior hypothalamus abolished thermogenic responses to cold stress. Clinical observations in man (Strauss and Globus, 1931; Davison and Selby, 1935; Alpers, 1936; Globus and Kuhlenbeck, 1942) supported the functional distinction of the two centres. Evidence was presented that destruction of the POAH by a tumour rendered patients hyperthermic, while destruction of the POPH made patients incapable of generating sufficient heat through metabolic processes, thus causing them to progress into hypothermia. It was therefore hypothesized, that the POAH was responsible for heat loss mechanisms (Bazett et al., 1933; Teague and Ranson, 1936; Magoun et al., 1938; Ranson and Magoun, 1939) and that the POPH was involved in thermogenic processes (Ranson and Magoun, 1939). The anterior hypothalamus was found to be thermosensitive and to respond to localized heating or cooling with appropriate heat loss or heat conserving and generating mechanisms (Barbour,

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1912; Hammel et al., 1960). Heating of the heat loss centre, for example, has been found to inhibit shivering and instigate vasodilation (Hemingway et al., 1940). Freeman and Davis (1959) have observed that the anterior hypothalamus of cats responds also to cooling as well as heating. Thermal stimuli to the anterior hypothalamus induced reciprocal rectal temperature changes, implying that certain defence mechanisms were activated. In contrast, they found that by conductive heating and cooling of the pre-optic posterior hypothalamus, rectal temperature followed the course of the temperature changes in the posterior hypothalamus, as opposed to acting in the opposite direction of the temperature change. The implications of this are therefore, that passive heating or cooling of the POPH does not invoke counteracting measures by the thermoregulatory centre.

The above findings suggest that the anterior hypothalamus is thermosensitive and exerts an inhibitory influence on the posterior hypothalamic centre (Hemingway et al., 1954; Birzis and Hemingway, 1957). Thermal stimulation of the POPH does not initiate either excitation of inhibition of the anterior hypothalamic centre. Therefore there exists only a unidirectional inhibition within the hypothalamus, that is the magnitude of inhibition imposed on the posterior hypothalamus by the POAH is either decreased or increased with cooling or heating respectively, of the heat loss centre. This central inhibition of thermogenesis (Benzinger, 1969) is contrary to the

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reciprocal inhibition theory as proposed by Meyer (1913).

The lack of response observed by cooling of the thermogenic centre, caused Hensel (1952) to suggest that the hypothalamus was responsive to only peripheral cold stimuli. Hammel et al. (1960) did however, succeed in eliciting thermogenic responses in dogs, during hypothalamic cooling only, without peripheral thermal stimulation.

The controversies arising from experiments utilizing surgical methods such as transections and 'piqure' needles, suggesting that bacterial infection as a result of the operation or an effect of anaesthesia was compounding the observations of body temperature changes, was resolved by Hemingway et al. (1940). They initiated shivering inhibition, vasomotor and panting responses in dogs with local heating of the hypothalamus by diathermy, thus leaving the hypothalamic structures intact and uninjured by their method. Using a similar method Euler (1950) observed changes in electric potential in the anterior hypothalamus, synchronous with the temperature changes induced by diathermy. Due to the size of the recording electrodes and the slow nature with which the 'temperature potentials' changed by as much as 5 - 10 mV, Euler excluded the possibility of summation of the responses of central thermoreceptors, as suggested by Adrian and Matthews (1934). Euler (1950) proposed that these 'slow temperature potentials' were a result of a transduction of thermal energy by temperature receptors. These 'slow potentials' should not be mistaken for the dynamic

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response of thermoreceptors, as shown in Fig. 2.2. Euler also suggested that these potentials may also be a result of potential changes in cells activated by thermoreceptors. These potentials were only obtainable from the anterior hypothalamus.

Shivering Centre

Several studies have indicated that shivering may be inhibited by thermal or electrical stimulation of the anterior hypothalamus (Hemingway et al., 1940; Freeman and Davis, 1959) and that ability of shivering inhibition is markedly impaired after bilateral lesions in the anterior portion of the lateral hypothalamus (Clark et al., 1939). Similar findings were noted after bilateral lesions to the caudal part of the anterior hypothalamus. Hemingway et al. (1954) found that the pre-optic region is very sensitive for inhibition of shivering in cats, but also observed that similar abolishment of tremor activity in skeletal muscle is attained whenever coordinated movement of these muscles is required.

Birzis and Hemingway (1956, 1957) clearly mapped out the efferent pathway of the shivering mechanism, earlier elucidated by Keller and Hare (1932) and Keller (1948). Birzis and Hemingway determined the shivering pathway to be in the midbrain, pons and medulla and demonstrated that the efferent pathways descend laterally within the reticular formation adjacent to the red nucleus and occupy the lateral portions of

the reticular formation within the pons and the medulla.

In the spinal cord, descending neurones from the shivering centre may synapse in the ventral roots with gamma motoneurones. It is hypothesized, that the hypothalamic centre activates shivering or involuntary muscular contractions at the spinal level by creating an instability of the stretch reflex via a change in the fusimotor activity (Thompson, 1970). The instability in the feedback loop is suggested to be the result of the inhibition of static and simultaneous excitation of dynamic motorneurones.

The rhythm of the shivering tremor, once shivering is activated by the hypothalamic centre, is thought to be generated at the spinal level (Hemingway, 1963). This has been validated by Kosaka and Simon (1968), who compared the shivering tremor induced by peripheral cooling to the tremor induced by spinal cord cooling in unanesthetized rabbits. They noted that frequency spectra for both tremors were identical. In humans the frequency of shivering tremor has been observed in the range of 7 to 12 Hz (Bawa et al., 1982).

During cooling of intact animals, two distinct features of shivering tremor have been observed, as hypothermia progresses. Initial periods of shivering are characterized by bursts of activity termed 'frisson reflexe' (Chatonnet and Tanche, 1956), which progressively becomes continuous and thenceforth termed 'frisson central'.

The difference in shivering observations between studies, as well as in subject variability may occur due to the rate of cooling imposed on the periphery. Dawson and Malcolm (1981) observed larger variations in colonic temperature of rats, when the rate of cooling was faster. Slow decreases in ambient temperature were also associated with the initiation of shivering tremor, but a stable colonic temperature was attained.

The interaction of core and peripheral temperature in the shivering mechanism has already been postulated by Lim (1960), while Bruck and Wunnenberg (1967a) suggested that mean body temperature may be the controlled variable. Lim (1960) eluded to the contribution of peripheral and core temperatures to the shivering mechanism in dogs. He observed that with respect to the initiation of shivering, peripheral temperature played a dominant role, whereas in terms of energy expenditure quantified from metabolic rate, the central temperature is three times as powerful as peripheral temperature.

Extrahypothalamic Thermoregulatory Structures

First evidence of spinal cord thermosensitivity was obtained by Bruck and Wunneberg (1966, 1967a, 1967b, 1970). They observed that spinal cord cooling, with no thermal stress to the periphery or hypothalamus, initiated shivering in guinea pigs, while conversely heating inhibited the shivering response. Further studies by Wunnenberg and Bruck (1968, 1970) on the

response characteristics of thermosensitive fibers in the spinal cord, demonstrated the existence of warm sensitive fibers in the spinal cord.

Studies conducted by Simon et al. (1965) in dogs and Simon and Iriki in cats (1970), confirmed the existence of warm sensitivity in ascending neurones in the spinal cord and demonstrated the characteristics of certain ascending neurones to spinal cooling. These investigations therefore suggested that neural fibres in the spinal cord exhibit static and dynamic responses to spinal heating and cooling. The static response of the warm and cold sensitive units resembled the static response of peripheral and central thermosensitive units (Simon and Iriki, 1971a, b), with the exception that the 'set-point' temperature seemed to be slightly higher than that of the peripheral temperature receptors, approximately 37°C and the maximum firing frequency of the cold sensitive units in the anterolateral tracts at C3 and C5 occurred at approximately 30°C as opposed to $20^{\circ}- 30^{\circ}$C for peripheral cold units (Zotterman, 1953) 1. The relevance of spinal cord temperature in thermoregulatory mechanisms has been disputed by Jessen et al. (1972). They observed that although intense heating of the spinal cord of oxen resulted in significant increases in heat loss and reduction in heat production, subsequent cooling of the spinal cord resulted in insignificant thermal responses. Jessen

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[1] The 'set-point' refers to the temperature at which the static firing rate of cold and warm receptors is similar in value and a decrease in temperature will enhance the resulting thermoregulatory drive

et al. (1972) suggest that the relevance of central cold thermosensitivity in thermoregulatory processes declines with body size. Spinal cord cold thermosensitivity would therefore be more relevant in smaller animals, such as the dog or cat, than in larger ones, as observed in the oxen.

Of primary importance is the role of the spinal cord in transferring peripheral and visceral thermal information to the central temperature centres in the hypothalamus. Classic theory suggests that the thermosensory pathway from cutaneous primary cold fibres enters the spinal cord through dorsal roots and synapses with secondary neurones, which cross over to the lateral side and subsequently ascend through the spinothalamic tract to the thalamus and hypothalamus. Although the lateral spinothalamic pathway has been confirmed as a major route for ascending neurones carrying information on the thermal state of the core and periphery, results reported by Norsell (1979) suggest that there exist several ascending pathways for cold and warm fibres, since unilateral and bilateral lesions, above the level of C2, of the lateral funiculi in the spinal cord of cats failed to result in thermoanaesthesia.

A recent study by Iggo and Ramsey (1976) suggests that there may exist separate ascending pathways from cutaneous cold receptors and cutaneous cold sensitive mechanoreceptors. Iggo and Ramsey (1976) reported the discovery of 'dorsal horn cold receptors', which are excited by peripheral cold stimulation, but do not respond when peripheral cold sensitive

mechanoreceptors are stimulated. It would appear that distinct pathways exist for handling information generated by mechanoceptors, nociceptors and thermoreceptors.

Whether the burst-frequency coded thermal information, generated by thermoreceptors, is transmitted along ascending spinal pathways unaltered, is not yet clear. This information may be modulated due to temperature induced changes of the characteristics of ascending spinal pathways. Suggestions for this have been made (Simon, 1972) based mainly on studies conducted on the membrane characteristics of spinal motoneurones. Rapid cooling of spinal motoneurones of the lumbosacral region in cats has been shown to affect the membrane characteristics by increasing the post-synaptic potenials (Pierau et al., 1969). Persistent and prolonged cooling resulted in a decrease in the resting membrane potential and consequently in increased excitability of the spinal motoneurones. Opposite effects were observed during rapid local warming. The thermal sensitivity of mammalian spinal motoneurones was found to be directly or indirectly related to the size of the motoneurones (Klussman et al., 1969). Membrane resistance of smaller neurones increased to a greater extent for a relative drop in temperature, compared to larger motoneurones.

During cold exposure, it is likely that the spinal cord temperature decreases due to conductive heat loss to the surrounding environment and tissues. On the basis of the above studies, it has therefore been implied that ascending spinal

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pathways may have similar thermal characteristics (Simon, 1972; Hammel, 1972) . This may result in the modulation of peripheral warm and cold signals at the spinal, thalamic and finally the hypothalamic level.

Through the work of Hinckel et al. (1983a,b), it is now evident that the brain stem is involved in the afferent thermoregulatory system. The nucleus raphe magnus seems to be involved mainly with the inhibition of shivering, while the dorsomedial subcoeruleus region was observed to instigate excitatory metabolic responses, as a result of electrical stimulation. The processing of thermal information within these structures is further discussed in the section reviewing neuronal models.

Interaction of Peripheral and Central Temperature Signals with Thermoregulatory Effector Mechanisms

It is evident from the discussion so far, that numerous thermosensitive structures play an important role in the thermoregulatory control system. The development of the hierarchical structure of the various control systems, which constitute the overall thermoregulatory system, has been attributed to the evolutionary process (Satinoff, 1978). As an organism progresses through evolutionary development, it also develops subservient control mechanisms, in parallel to the central thermoregulatory system (Satinoff, 1978). Satinoff

suggests, that evolution does not transfer minor control functions from the spinal cord and midbrain to the pre-optic hypothalamus, but instead new control loops are developed in parallel with the existing system. In instances where the control loops at the bottom of the hierarchical arrangement fail to function properly, the central control mechanism could take over in attempting to attain normothermia.

The interaction of thermal drives from the periphery, spinal cord and hypothalamic structures is still a controversial issue. It is well documented that temperature changes in these areas, if they are in the same direction, will enhance thermoregulatory responses and if the changes are in opposite directions, then relative inhibition of these responses will occur (Hensel, 1982). The dispute arises, when determining whether the neural drives for these effector mechanisms, originating peripherally and centrally, are additive (Hammel, 1968) or multiplicative (Bruck and Wunnenberg, 1967a,b), or a combination of the two.

Simon (1972) has observed that the neural output from thermosensitive units in the spinal cord is modulated by the output from cutaneous thermoreceptors. He observed that skin cooling of cats increased the activity of spinal cold units and inhibited the discharge of the warm units in general, although some warm units were found to be unaffected by the peripheral thermal stimulus. Peripheral heating did not elicit distinct responses from spinal warm units, although an increase in

activity was observed from several cold units. The latter may be attributed to the paradoxical response of cold receptors at high and relatively noxious temperatures, giving rise to the 'paradoxical' sensation of cold in humans, at temperatures above 45°C. Simon explains the variety of responses of spinal warm units to peripheral heating as an indication that different populations of cutaneous warm receptors were stimulated. Also, since the skin temperature of furred animals is usually the same or slightly higher than core temperature, the role of peripheral warm receptors may not be a dominant one in their thermal control loop.

The interaction of spinal and hypothalamic signals seems to be more complex. Although several thermosensitive structures have been identified in the hypothalamus, Guieu and Hardy (1970) suggest that a distinction should be made between pre-optic anterior 'thermodetectors' and temperature sensitive interneurones in the same region. The temperature sensitive interneurones, may not necessarily be involved in thermal sensory receiving, processing or effector mechanisms.

The contribution of both regions, POAH and POPH, in the stimulus-response relationship seems to be equivalent with respect to thermoregulatory effector mechanisms (Jessen and Mayer, 1971). Furthermore, Jessen and Ludwig (1971) and Jessen et al. (1968) have shown that signals from spinal and central structures are additive to yield appropriate thermogenic or thermolytic responses. The nature of the interaction of deep

core temperature detectors (i.e. abdominal) and spinal temperature sensitive units is not yet established.

A great deal of emphasis has so far been placed on the importance of an intact connection between hypothalamic centres and the spinal cord for the maintenance of normal body temperature. A study by Lin and Chai (1974) suggests that other structures in the CNS, such as the medulla oblongata, may be involved in thermoregulation. Poulos and Molt (1976), investigated static and dynamic responses of cold and warm receptors in the medulla, thalamus and trigeminal ganglion of the cat and monkey and found the responses to be similar to those seen in cutaneous temperature receptors. The 'set-point' as defined previously, was shifted to higher temperatures for the central receptors. This suggests that there exist numerous relay structures for thermal information in the CNS. The ability of these structures for processing thermal information and instigating appropriate thermoregulatory effector mechanisms is yet to be determined.

III. Physiology of Cold Water Immersion

Numerous reports pertaining to accidental hypothermia suggest there is, as yet, no optimal management of victims suffering from profound hypothermia (Laufman, 1951; Freuhan, 1960; Blair, 1969; O'Keefe, 1977; Stine, 1977). The majority of incidents reported involve immersion in cold water (Bangs, 1970; Jessen and Hagelstein, 1972; Golden and Rivers, 1975; Keatinge, 1977). Such conclusions can only portray a lack of experimental data on the progression of humans into a state of hypothermia. Problems concerning body core cooling in cold water diving have only become emphasized in recent years, (Webb, 1973; Keatinge and Hayward, 1979).

The main physiological changes from normal, that would be encountered and also be visible upon cooling of the body core are outlined in Fig. 2.4.

Much of the initial information on human exposure to cold has been provided in the form of case studies of hypothermia victims, as reported by the physicians attending such emergencies (Laufman, 1951; Marshall and McCaughey, 1956; Linton and Ledingham, 1966; Kugelberg et al., 1967; Lash, 1967; Phillipson and Herbert, 1967; Anderson et al., 1970; McKean et al., 1970; Tolman and Cohen, 1970; Truscott et al., 1973). Some information on the human experiments conducted in Nazi concentration camps in Dachau and Auschwitz during World War II,

Fig. 2.4 : The onset of various clinical features of
    hypothermia, with respect to core temperature. From Maclean
    and Emslie-Smith (1977).

RISK OF –

Transient benign supraventricular or ventricular dysrhythmias

Ventricular fibrillation

Death (failure to revive)
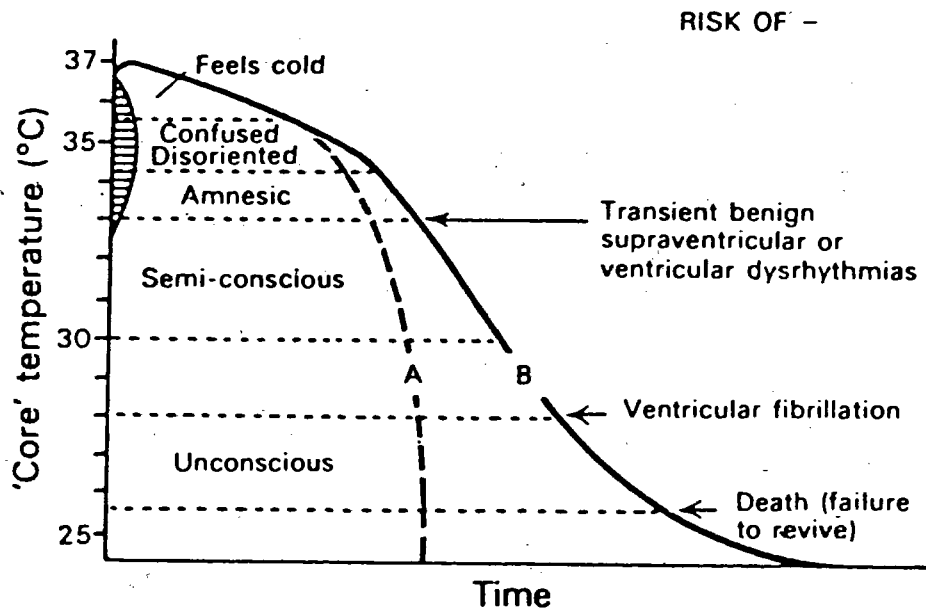
CLINICAL SIGNS –

Reluctance to communicate

Muscle rigidity

Pupils dilated

Tendon reflexes absent
Respiration depressed
Intense vasoconstriction
Profound bradycardia
    (vasodilatation)
Acute heart failure
Rigidity abolished

'Core' temperature (°C)

37 — Feels cold
35 — Confused Disoriented
    Amnesic
    Semi-conscious
30 —
    A   B
    Unconscious
25 —

Time

has been reported by Alexander (1945). However, due to the physical condition of the subjects, the nature of the experimental procedure, and in view of the ethical considerations, data obtained from these brutal experiments is not usually used as a source of reference in thermoregulatory studies. As Swan (1974) summarizes:

> "whatever benefit might have accured to science from this gruesome experience was not harvested".

Vasomotor Response

The initial response to cold water immersion is intense vasoconstriction (Pappenheimer et al. 1941). This immediate increase in peripheral vascular resistance will cause a rise in venous and arterial blood pressures. Such a load on the cardiovascular system may cause death in some cases (Hervey, 1973), especially older people, where the exposure has not been long enough to result in classic symptoms of hypothermia.

During immersion in waters of freezing temperatures, the initial vasocontriction will eventually be followed by vasodilation (Lewis, 1930). Prolonged exposure will result in an alternating vasoconstricting-vasodilating mechanism in peripheral circulation of the extremities, a phenomenon known as the 'hunting reflex'. The hunting reflex is thought to be a defense mechanism preventing tissue damage, due to lack of blood supply. Bazett et al. (1948) and Bazett (1949a) suggested, that the vasodilation is caused by paralysis of the smooth muscles of

the arterioles, as a result of the cold stimulus. The re-instated blood circulation increases the temperature of the surrounding tissue and consequently increases heat flow from the extremities. Once the temperature of the smooth muscles is raised, sufficiently to eliminate the paralysis, a vasoconstrictor tone is again instigated. The above process is continuously repeated during the exposure. Folkow (1955) suggests that the 'hunting reflex' is a result of a pain fibre axon reflex. At extremely low temperatures, the pain fibres and not so much the cold fibres, will be stimulated, thus possibly instigating an axon reflex vasodilation. His theory proposes that subsequent warming of the tissue due to increased blood flow, eliminates the pain fibre discharge and concomitantly the axon reflex vasodilation. The latter would allow the tissue temperature to drop, thereby invoking the pain receptor discharge and vasodilation.

Chronic exposure to cold eventually causes necrosis of muscle tissue due to lack of oxygen (Laufman, 1951). The more familiar example, is one of prolonged exposure to cold and moist environment leading to necrosis of the voluntary muscles of the feet, known as 'immersion foot' or 'trench foot' (Marshall and McCaughey, 1956). Immersion foot was reported as a serious problem in infantry during the first World War.

Metabolism

The metabolic response in man to whole body cooling is a defence mechanism, whose function is to maintain normal body core temperature. The response will be different for a rapid cooling situation leading to acute hypothermia, than for a chronic exposure to cold. When discussing prolonged cold exposures, various indices of acclimatization have to be considered.

In general, during cold stress, homeothermic mammals produce additional heat through :

- voluntary muscle activity, which comes under the auspices of behavioural thermoregulation.
- involuntary muscle activity, tonic or rhythmic in nature, known as shivering.
- non-shivering thermogenesis, involving the production of heat through increased metabolism of brown adipose tissue (BAT) deposits. Non-shivering-thermogenesis has been demonstrated in neworn infants, due to their brown fat deposits in the interscapular region, but is abolished in part a few weeks after birth (Sinclair, 1978).

Rapid cooling results in marked elevation of metabolic rate in humans. The metabolic response consists of two main components (Benzinger, 1969; Hayward et al., 1977). At the onset of cold water immersion, Benzinger (1969) and Hayward et al. (1977) observed a metabolic overshoot, which subsequently subsided to levels slightly higher than that of resting values. Since core temperature, measured either rectally (Hayward et al., 1977) or in the tympanum (Benzinger, 1969) does not begin to drop at this early stage, the initial dynamic overshoot has been ascribed to the peripheral cold receptor drive. The hypothesis forwarded by Benzinger suggests that the magnitude of the overshoot is representative of the thermal gradient between skin and water.

As the skin temperature approaches a steady state value, slightly higher than the temperature of the water, the metabolic overshoot subsides (Fig. 2.5). The metabolic rate then begins to rise slowly, in response to a decreasing core temperature. As can be seen from Fig. 2.6 the theory of central inhibition of thermogenesis (Benzinger, 1969) proposes that there exists a constant excitatory drive from the peripheral cold receptors to the thermogenic centre in the pre-optic posterior hypothalamus, the magnitude of which is determined by the thermal stimulus perceived by the peripheral cold receptors. However, the output from the heat production centre is inhibited by the heat loss

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Fig. 2.5 : Relationship of skin and core temperatures to
metabolic rate (mean s.e.) for five subjects cooled for 60
minutes. From Hayward et al. (1977).

47b
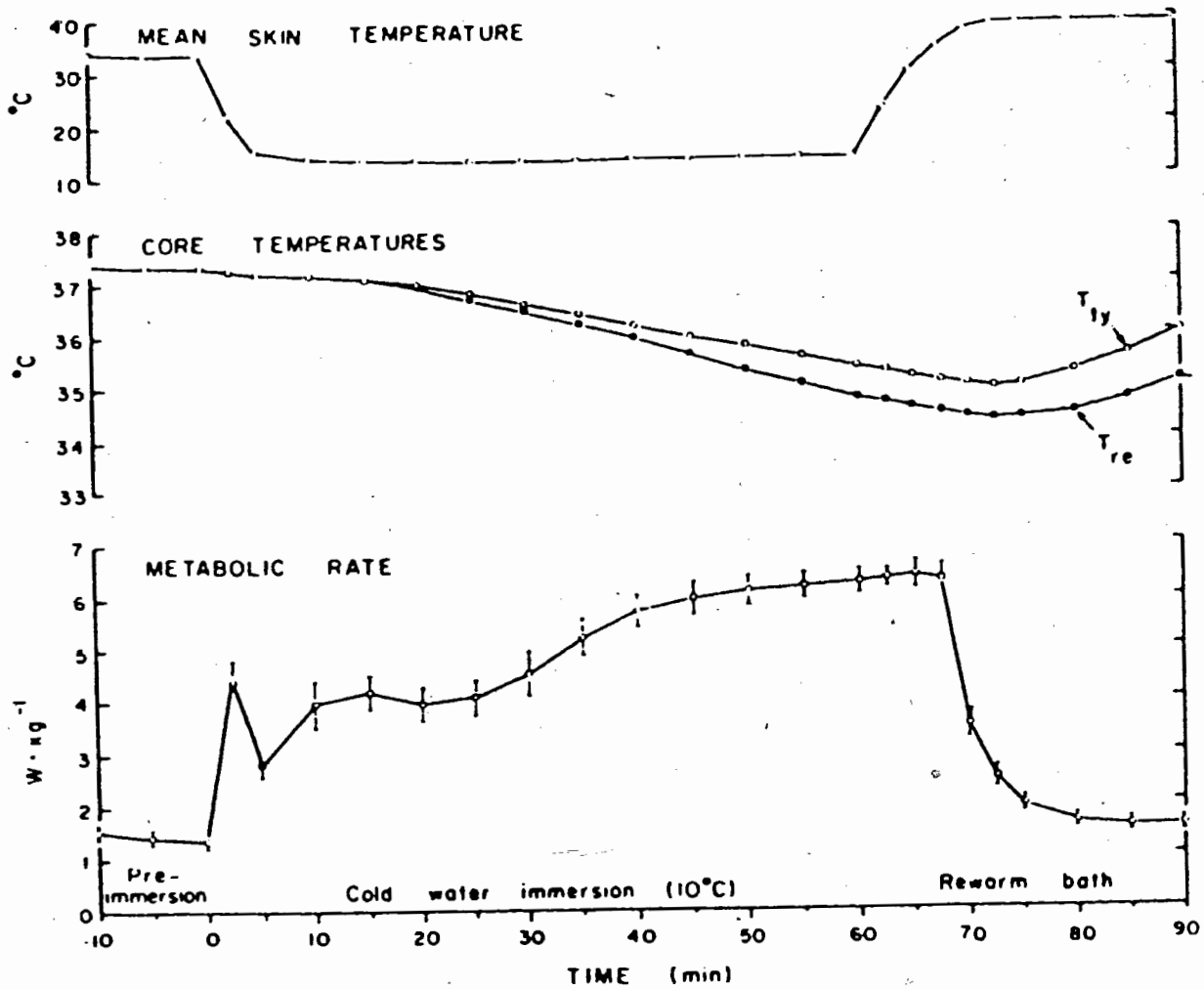
Fig. 2.6 : The thermoregulatory centres in the hypothalamus. See text for explanation of diagram. From Benzinger (1970).

sweat glands

cutaneous blood
vessels

metabolism
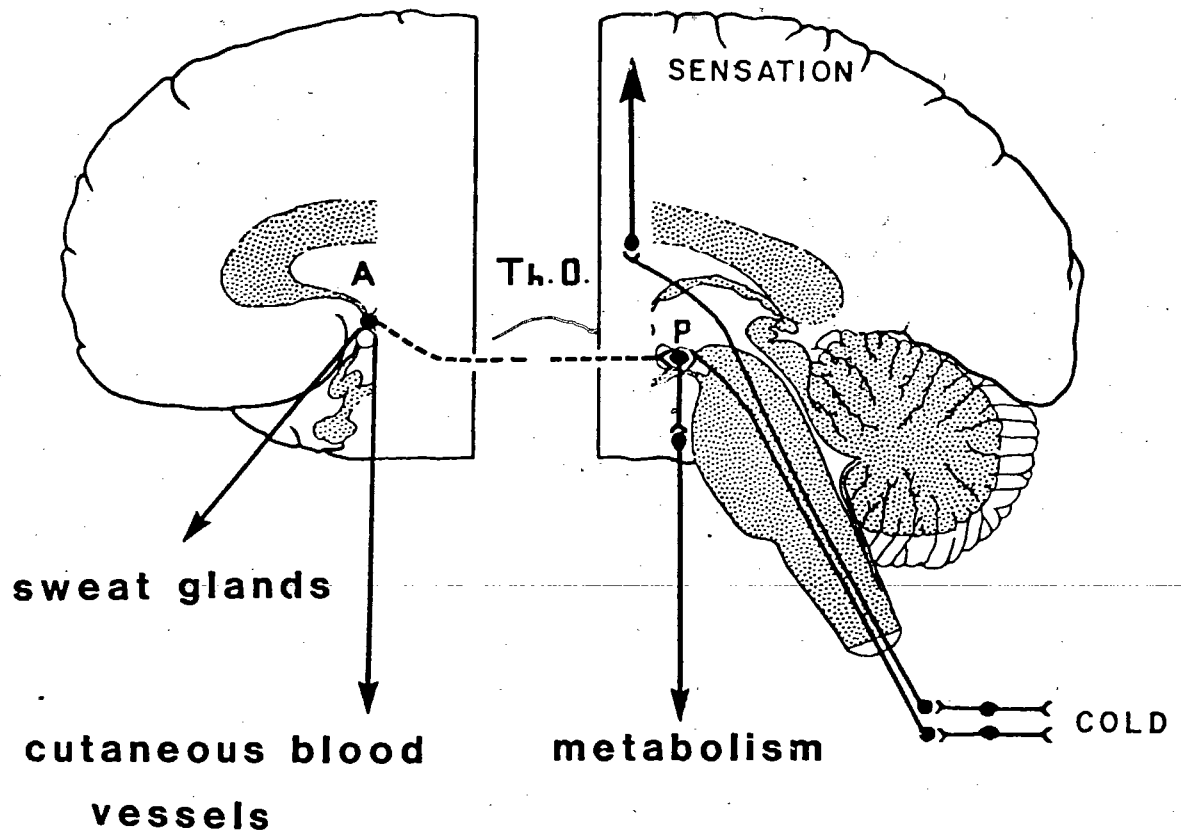
centre (POAH); again the magnitude of inhibition being dependent on the temperature at the heat loss centre. As core temperature decreases, there is also a decrease in the inhibitory stimulus, resulting in an increased output from the heat production centre, as measured by the consumption of oxygen.

Benzinger proposes that the metabolic rate after the initial overshoot is independent of skin temperature, as long as the tympanic temperature is maintained above a certain set point temperature, approximately 37.1^{o}C (Fig. 2.7). Once the tympanic temperature falls below this controversial temperature, metabolic rate rises along an isotherm, whose parabolic rise will be a function of the excitatory drive from the peripheral cold receptors. The nature of the metabolic response due to core cooling, at a certain skin temperature (as suggested by Benzinger) has been contradicted by the findings of Craig and Dvorak (1966), who observed a fairly linear relationship between metabolic rate and tympanic temperature at various bath temperatures. Whether the rate of cooling of core temperature was the significant factor underlying these discrepancies is not evident from these studies.

From a physiological perspective, the metabolic response to changing core temperature as suggested by Benzinger (Fig. 2.7) seems more acceptable, as it follows the bell-shaped curve characteristic of the neural drive from skin cold receptors, at those temperatures as indicated in Fig. 2.8 (Hensel, 1976b).

Fig. 2.7 : Set point characteristics of chemical
thermoregulation. With skin isotherms added, chemical
thermoregulation seemed to be dependent on skin cold
receptor excitation and central warm inhibition. From
Benzinger (1970).

50b
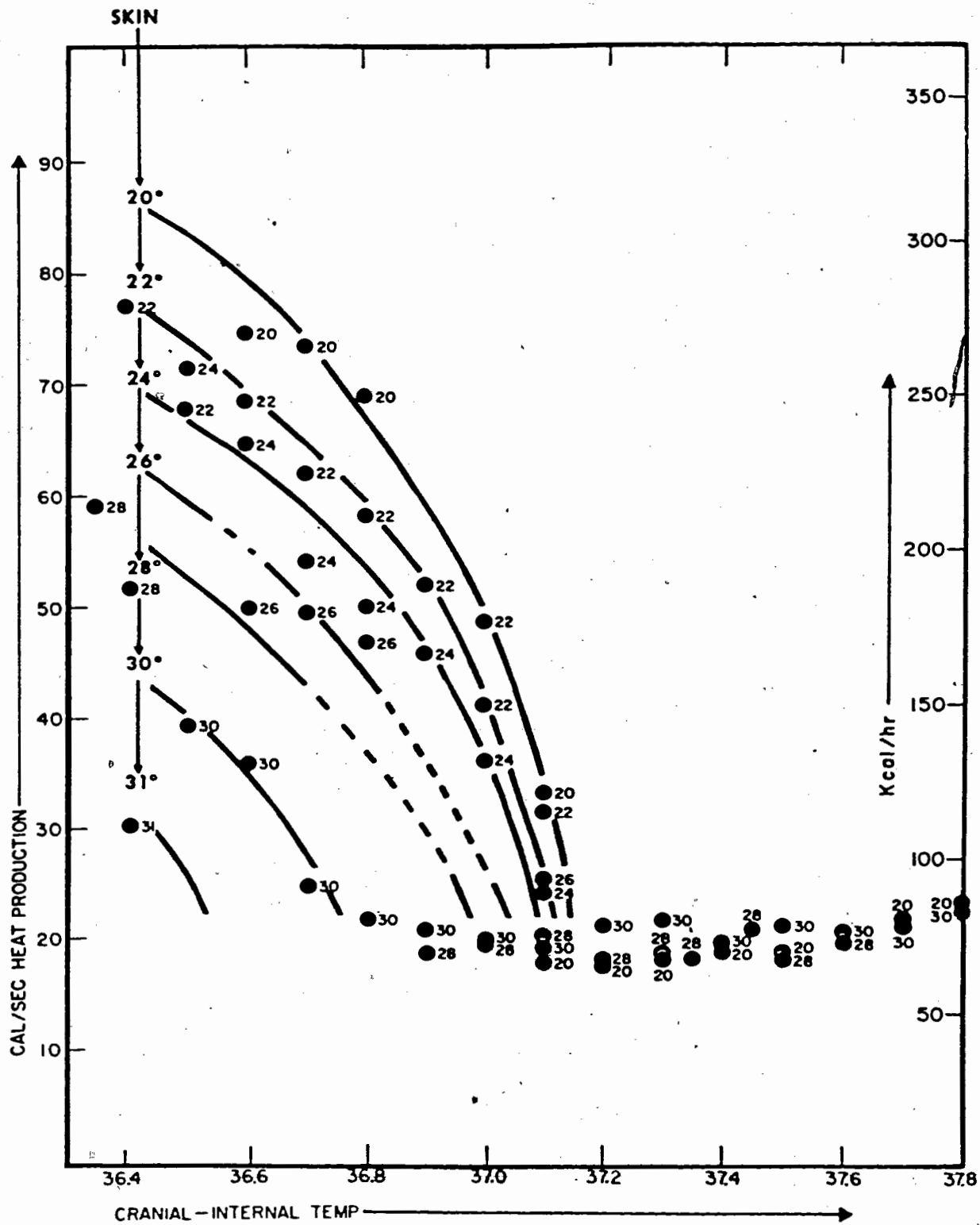
Fig. 2.8 : Comparison of the average static frequency of cold
    fibres in monkeys (Dykes, 1976; closed circles) and
    metabolic rate in man (Benzinger, 1969; open circles), as a
    function of skin temperature. Adapted from Hensel (1976b).

51b
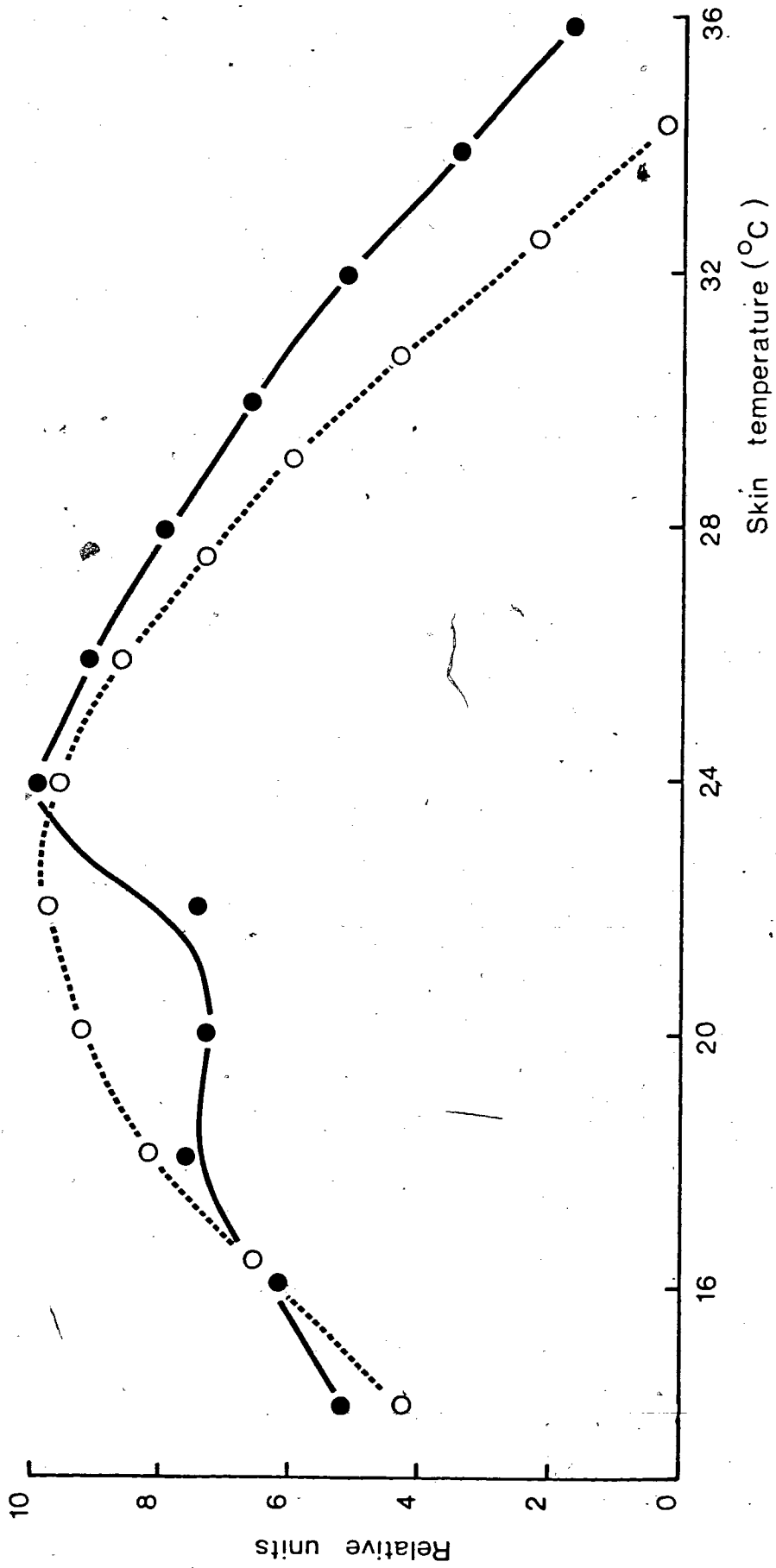
With decreasing core temperature, the increase in oxygen consumption is directly related to the metabolic cost of shivering (Horvath et al., 1956). The onset of shivering is dependent on skin temperature, and with progressive cooling of the core, the intensity increases. In adults, the pattern of shivering involves the muscles of the neck, abdominal cavity and pectoral regions and eventually the muscles of the extremities. With further cooling towards mild hypothermia (35^OC core temperature), there is generalized shivering.

The metabolic response has been shown by Nadel et al. (1970) to be a function of peripheral cooling and recently, Piantadosi (1981) investigated core cooling in a hyperbaric environment and suggested that the observed oxygen uptake is a function of the rate of drop of rectal temperature.

Although in rapid immersion hypothermia, elevations of oxygen consumption are usually associated with shivering thermogenesis, Horvath et al. (1956) observed increases in oxygen consumption, VO2, up to 293 ml. over basal levels before the onset of shivering. The total oxygen debt developed by their subjects after being exposed to ambient air temperature of -3^OC was 1200 ml., suggesting that part of this was required to pay the debt developed by anaerobic metabolism and part of it required to pay the heat debt accrued during the period of cold exposure.

Metabolic Response to a Thermal Stimulus Exciting Peripheral
Pain Receptors

The metabolic response due to pain receptor stimulation has
not been subject to much scrutiny in thermoregulatory studies.
It is known that temperature extremes invoke sensations of pain.
Guyton (1976) suggests that pain receptors begin to fire at
temperatures below $15^{O}C$ and above $45^{O}C$. If the temperature is
either decreased in the former case, or increased in the latter,
pain receptor discharge frequency will increase exponentially
(Guyton, 1976), presumably to a point where tissue damage
occurs.

In many cold water experiments discussed, water
temperatures were below $15^{O}C$, implying a discharge from both
cold and pain receptors. Stressor stimuli eliciting pain act
through afferent neurones, on the hypothalamus, causing a
discharge of corticotropin releasing factor (CRF) and
subsequently the release of adenocorticotropin hormone (ACTH)
from the pituitary gland (Yates et al., 1980). It has been shown
that CRF not only causes the release of ACTH from the pituitary
gland, but also stimulates ACTH synthesis in the anterior lobe
of the pituitary (Brooks and Koizumi, 1980). The
adenocorticotropin hormone once released, stimulates the
secretion of epinephrine from the adrenal cortex, the response
being dependent upon blood glucose levels (Hokfelt, 1951; Duner,
1953; Euler and Folkow, 1953). Moderate secretion of epinephrine

has been found to elicit extensive metabolic effects in skeletal muscle and liver cells (Celander, 1953, 1954; Euler, 1953). Although low levels of epinephrine dilate vessels of the muscles and liver (Folkow, 1955), the response to higher concentrations is vasoconstriction. The vasoconstrictor tone due to high epinephrine concentrations is followed by a prolonged vasodilatory effect (Barcroft and Swan, 1953), suggested to be secondary to the metabolic effect of epinephrine on skeletal muscle. As epinephrine stimulates carbohydrate and lipid metabolism, there will be a resultant increase in lactic acid levels. Due to the intense vasoconstricting action of epinephrine, lactic acid washout from the muscles will be minimal and there will be a local effect of lactic acid to dilate the vessels (Lundholm, 1956).

Epinephrine has been shown to have different effects on smooth muscle (White et al., 1973), it induces contraction of the ileocal and pyloric sphincters, relaxation of gastrointestinal tract and dilation of bronchial musculature. Norepinephrine, in contrast, exerts weaker stimuli.

The action of epinephrine during extreme cold exposure may therefore be quite prominent in terms of oxygen consumption. Epinephrine promotes glycogenolysis in muscle and liver, resulting in elevation of the blood glucose level and lactic acid levels. There is a concomitant 20 - 40% increase in oxygen consumption in man (White et al., 1973) with even greater increases in carbon dioxide production, thus elevating the

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respiratory quotient.

Epinephrine also has a profound effect on lipid metabolism, resulting in increased oxygen utilization. In contrast, the influence of norepinephrine on carbohydrate and lipid metabolism is only a fraction of that of epinephrine.

The onset of elevations in metabolic rate due to pain receptor stimulation can only be speculative, as there is insufficient evidence available. A table of time constants for the separate pathways in this system has been reported by Yates et al. (1980) and presented in Table 2.1. The time constants for neural stimulation of CRH release, CRH stimulation of ACTH release and the delay in adrenal response to ACTH are all below one minute. Taking into account that the circulation time for hormones in blood is less than 15 seconds, the total stimulus-response time could possibly be less than four minutes. The question remains as to the contribution of this mechanism to the metabolic response observed during cold water immersion. Does this response contribute to the initial metabolic overshoot at the onset of immersion, thought to be mainly a result of peripheral cooling rate, or is it involved in the later elevations in metabolic rate, associated usually with core cooling?

Table 2.1 : Time domains in adrenal glucocorticoid system
     (adapted from Yates *et al*., 1981).

Process	Estimated longest (dominant) time constant*
ACTH metabolism	10 min.
Delay in adrenal response to ACTH	1 min.
CRH stimulation of ACTH release	1 min.
Neural stimulation or inhibition of CRH release	1 min.
Circulation time for hormones in blood	15 secs.
Binding of cortico-steroids by plasma proteins	1 sec.

* the time required for a process to reach 62.3% completion, a value equal to the fraction $(1 - 1/e)$; values will depend on species and sometimes on the sex of the subject. The numbers are best estimates for the human being.

(adapted from Yates et al., 1980)

Metabolic Response to Prolonged Exposures to a Cold Stimulus

Information on the effect of prolonged cold water immersion
in humans is sparse and is mainly contained within case
histories of hypothermia accidents, maritime disasters and
reports on the Nazi experiments. Shivering thermogenesis is
reported to be abolished at approximately 32°C core temperature,
Fig. 2.4, leading to a reduction in oxygen consumption. At
extremely low core temperatures, muscle rigidity becomes
predominant (McClean and Emslie-Smith, 1977).

Cold Adaptation

Man is often termed a 'tropical animal', inferring he could
only survive comfortably without protection from the environment
in warm, moderately humid climates. The fact that man has been
able to populate areas, vastly diverse in their ambient
conditions, demonstrates his thermal adaptability. The standard
method of demonstrating adaptation of man to a chronic cold
exposure is to gauge the changes in physiological parameters
from pre- to post-exposure to the cold environment. .

The benefits of behavioural adaptation to acute cold
exposures have been reported by Hayward et al. (1975b). They
found that during acute cold water immersion, cooling rate was
significantly reduced, if individuals maintained an 'embryonic'

position', thus decreasing heat loss from high heat loss areas, such as the side of the chest and groin.

A striking example of behavioural adaptation, is the clothing worn by Eskimos (Folk, 1974). Their parkas are designed to maintain a fairly warm microclimate. If heavy work is required, it can be modified to permit a circulation of air, thus preventing condensation and a rise in temperature of the microclimate.

Scholander et al. (1958) have observed significant physiological changes in a group of young men exposed to a chronic cold stress for several weeks, in the Norwegian mountains. The adaptation has been attributed to mildly vigorous activities of these individuals during the daytime. Although the level of activities was not monitored, it can be argued that these individuals attempted to maintain thermal comfort by increasing heat production through their physical activities, since they were restricted from wearing warm clothing.

The trend in this type of adaptation is to achieve a level of thermal comfort which is tolerable. Scholander et al. (1958) have found that, although the intensity of shivering decreased during sleep over the chronic exposure, after the acclimatization was established, the subjects tolerated this activity and their sleep was not disturbed by it.

In comparison, the Australian Aborigines do not show significant changes in metabolic rate (Hensel et al., 1973), but allow their skin temperatures to drop considerably lower than

their counterpart white controls, thus establishing a much greater insulative layer. The lack of metabolic response in the Australian natives, causes their core temperature to drop to mildly hypothermic levels. Their adaptation is therefore one of 'insulative-hypothermic', whereby the insulative layer is increased and decreased body temperature is tolerated.

In cold acclimatized individuals, such as the Korean ama (Hong, 1963), the threshold for shivering is significantly reduced to lower core temperatures. This has also been observed in laboratory acclimatized guinea pigs (Bruck and Wunnenberg, 1970).

Banet et al. (1978) observed that prolonged intermittent exposure of rats to cold environments offset the metabolic rate to higher values. The magnitude of the shift in metabolic rate towards higher values was constant for a range of ambient temperatures, as illustrated in Fig. 2.9. However, when only the spinal cord was subjected to prolonged intermittent cooling, there was an increase in the gain of the metabolic response. This is observed as greater increases in metabolic rate at lower ambient temperatures.

Adaptations to cold stress have also been observed in localized areas of the body. Immersing the hand in cold water increases systolic and diastolic pressure, heart rate and decreases the skin temperature (Le Blanc, 1978). If the temperature of the water is close to freezing, the hunting reflex (discussed earlier) will be elicited. In normal

Fig. 2.9 : Average oxygen consumption at various temperatures in
    rats after prolonged intermittent spinal cord cooling
    (closed circles), after prolonged intermittent exposure to
    cold ambients (open circles) and in controls (open
    triangles). From Banet et al. (1978).

60b
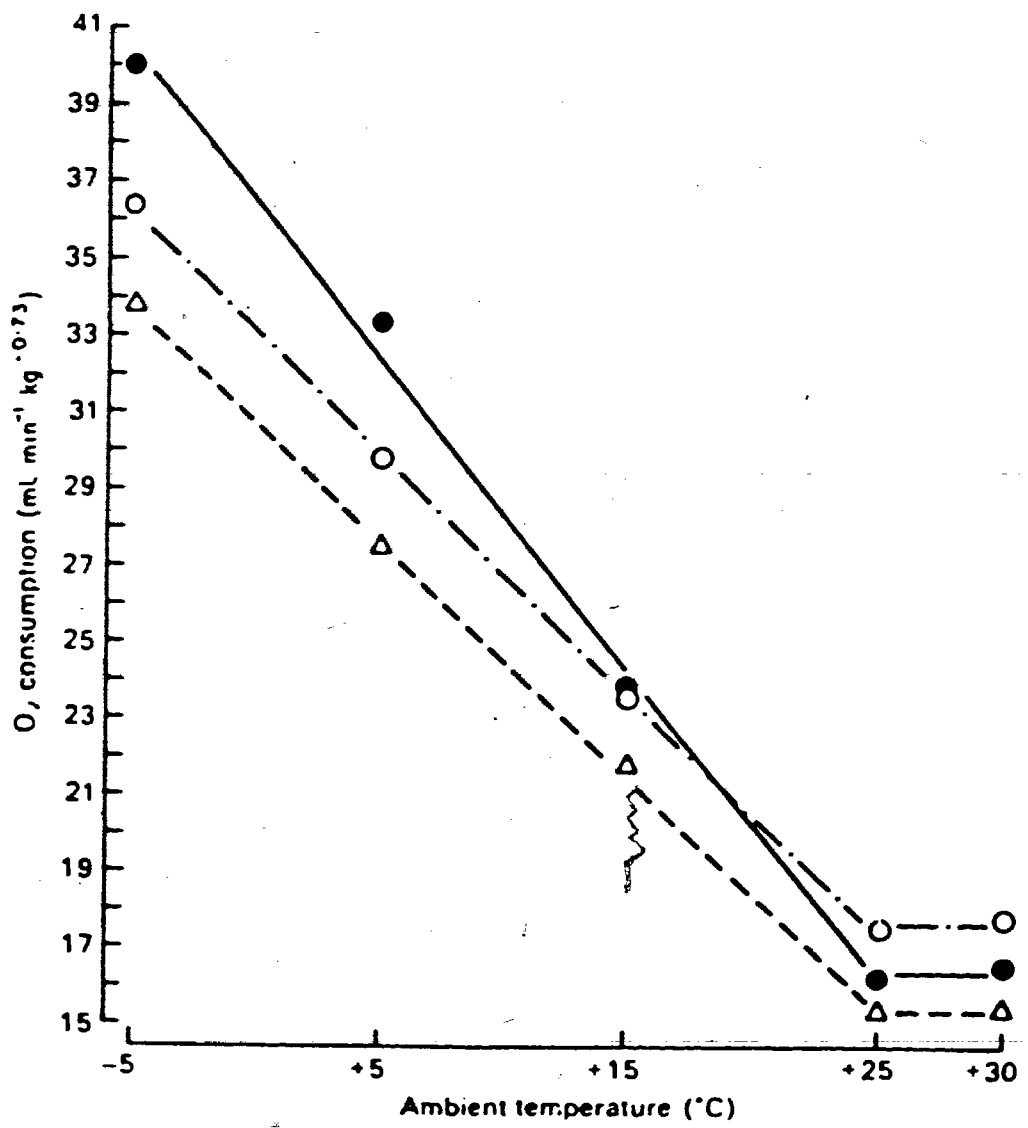
individuals, such an immersion would also induce a sensation of pain. The above responses were observed in Gaspe fishermen (LeBlanc et al., 1975) and acclimatized individuals (Le Blanc and Potvin, 1966) and compared to the responses of unacclimatized individuals. The results of the comparisons of these responses are similar; acclimatized individuals were observed to have lower diastolic and systolic pressures, as well as heart rates, in response to cold water immersion, than the unacclimatized individuals undergoing the same hand immersion trials.

Le Blanc (1975) also compared the systolic pressures during a hand immersion test of Eskimo adults and children with a control group of white men. His results indicate no substantial differences within the Eskimo group, however the control group had markedly higher systolic blood pressures than the Eskimo group.

In infants, the lack of response of some effector mechanisms may be partially due to the fact that the thermoregulatory system as well as other neural structures are still in the developmental stage. Doi and Kuroshima (1979) investigated the effect of cold acclimatiztion of infant rats, on their thermogenic response in adulthood. They found that infant rats exposed for two weeks to -5°C ambient air four hours daily, showed signs of acclimatization 18 weeks post exposure, when compared to controls taken from the same litter. When comparing rats acclimatized in infancy and rats acclimatized in

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adulthood, they observed that the rats acclimatized in adulthood only retained signs of acclimatization 4 weeks post adaptation. The rats acclimatized in infancy exhibited an inhibition of shivering thermogenesis. They postulated that cold exposure in infancy coincided with the development of hypothalamic centres. The cold exposure may have accelerated myelinization of neural fibres and subsequently a faster development of the thermoregulatory system. This has been observed by Buchanan and Hill (1947) who noted that the development of the thermoregulatory system coincides with enhanced myelination of the hypothalamus. Doi and Kuroshima (1979) also suggested that the cold stress may enhance the hypothalamus-pituitary- adrenal response, thus increasing the activity of the epinephrine-synthesizing system. The sensitivity to ACTH and glucocorticoids may be greater in infancy, gradually declining towards adulthood, thus maintaining higher levels of activity as a result of cold exposure in infancy.

Adaptations to cold spanning several generations would evolve into genetic adaptations to cold. This type of adaptation would have the slowest time constant and would involve several generations (Hensel, 1982), therefore being the most difficult to quantify.

IV. Thermoregulation Models

Numerous attempts have been made to simulate the maintenance of normothermia in humans. Initially, the main emphasis was to establish equations governing the stimulus-response relationship of the human thermoregulatory effector mechanisms. This allowed for various predictions of cooling rate (Hayward et al., 1975a), survival time (Molnar, 1956) and metabolic response (Hayward et al., 1977), given a certain temperature of water.

Hardy (1972) suggests that various 'verbal' and 'pictorial' models were first attempts of modelling thermoregulation. The intensified research in the area over the last few decades has given rise to numerous models. These models simulate the human thermostat as a complex control system, with multiple input signals. In contrast, stimulus-response equations do not attempt to analyse the individual networks comprising the thermoregulatory system, but in the simplest form, derive regression equations from empirical stimulus-response data.

Stimulus-Response Equations

From numerous reports of survival after long term exposure in cold water, as a result of maritime disasters, Molnar (1956) constructed a set of tables predicting the probability of survival in various water temperatures. Since his chart is a graphical representation of the information on survival times available, it is not necessarily indicative of the general population. It would be representative of the individuals who survived a certain exposure time, disregarding the number who perhaps succumbed to the exposure. One anomaly of his chart is the prediction of survival for infinite exposure time in waters of 23.8° C (75° F) temperature. Beckman et al. (1966) observed experimentally that their subjects could tolerate a water temperature of 75° F for only an average of 8.1 hours. The tolerance charts for predicting survival in cold water and life raft exposures have recently been updated by Hall (1972). In the construction of water immersion tolerance normograms, Hall accounted for the decrease in thermal insulation due to wetting and hydrostatic pressure in clothed subjects.

The above mentioned normograms are a gross generalization and are perhaps indicative of the response of a small population. The individual differences in survival time are evident from findings of Keatinge (1960), who found a high correlation between the cooling rate of rectal temperature and the reciprocal of the skinfold thickness. To account for body

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size and body composition, Sloan and Keatinge (1973) accounted
for surface-area/mass ratio in addition to the skinfold
thickness and found improvement when correlating these parmeters
to core cooling rate. Smith and Hames (1962) suggested that
equations dealing with heat loss to the environment, should
incorporate surface area as well as insulative values of the
clothing.

Hayward et al. (1975a) derived a set of equations from
their immersion studies relating survival time with water
temperature and similarly predicting cooling rate of rectal
temperature. Hayward et al. (1978) also developed equations to
include terms related to subject somatotype. They found a high
correlation between cooling rate and subjects' ectomorphic
component. The correlation was higher when including all three
components of the somatotype in a ratio. Hayward et al. did not
however incorporate the water temperature and somatotype
components into one model, to predict core cooling rate.

As discussed earlier, shivering thermogenesis is a major
response to core cooling, evidenced by visible involuntary
muscular contractions and increased oxygen uptake. Since
immersion in water affects peripheral and core teperature,
several studies have attempted to relate metabolic processes
with peripheral and core temperature. Burton (1934) applied the
theories of heat flow to predict energy metabolism from a body
subjected to environmental extremes. His predictions incorporate
internal body and ambient temperature as well as an index of

insulation. Burton emphasizes the importance of kinanthropometric variables of size, age and sex in determining the energy metabolism of humans. Burton's analysis deals mainly with stable conditions and does not deal specifically with temperature extremes and water immersion.

With the development of the 'set-point' theory of thermoregulation, several authors attempted relating energy metabolism in response to cold exposure by simulating the operation of one or more thermostats in parallel. In essence, the set point theory (Bazett, 1949; Hammel et al., 1963; Vendrik, 1959) suggests that observed responses to a change in environmental temperature are a function of the deviation of the temperature from a set point temperature. To account for metabolic responses observed by changing skin temperature with steady state core temperature, and changing core temperature with constant skin temperature, the existence of two set points was hypothesized (Hammel et al., 1963), as shown in Equation 2.1

$$R = a (Th - Th0) + b (Ts - Ts0) \qquad \dots (2.1)$$

where,

R = response

a, b = proportionality constants for heat dissipating and heat conserving mechanisms.

Th = hypothalamic temperature

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Ts   = mean skin temperature,

Th0   = reference hypothalamic temperature = 37 °C

Ts0   = reference skin temperature = 33 °C

Whether the core and peripheral terms are additive or multiplicative is hypothetical. For metabolic rates above resting values, a multiplicative relationship has been suggested by Stolwijk and Hardy (1966) and Hayward et al. (1977). Jessen and Ludwig (1971) observed experimentally that thermal signals generated in the spinal cord and hypothalamus are additive, to result in a combined effector mechanism such as respiratory evaporative heat loss and heat production.

There is also no standardization for the values of the two set point temperatures and proportionalty constants. Controversies surrounding set point values will perhaps be resolved with more physiological evidence and a more adequate explanation of an adjustable set point.

Nadel et al. (1970) suggest the inclusion of an additional peripheral term, which could account for increased response to peripheral stimuli without core temperature changes.

The above studies deal mainly with situations of cold water immersion. Timbal et al. (1976a, 1976b) compared the metabolic response to cold air exposure as opposed to water immersion. Their predictive equations suggest that peripheral temperature is the main drive to the metabolic response in cold air

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exposures, while predictions for water immersion should take into consideration core temperature. They also recognize the relative significance of the rate of change of peripheral temperature.

Engineering Models

In early attempts at solving the thermodynamic processes within the body the analysis was simplified by either considering one cylindrical component of the body (Pennes, 1948) or by considering the entire body as a cylinder (Wyndham and Atkins, 1960). The single cylinder approximation of the human body is based on the core and shell principle (Machle and Hatch, 1947; Aschoff and Wever, 1958) and involves partitioning the cylinder into several concentric layers.

Recent models analyse the human thermal system by segmenting the body into a series of cylindrical components, each having a specific blood flow and metabolic rate (Wissler, 1961, 1970). The transfer of heat between adjacent cylinders by circulating blood, the counter current heat exchange principle, and conduction, is accounted for.

The numerous models that fall within the above category have been classified by Hsu (1971) as those that simulate a steady state response and those that are capable of solving thermodynamic responses during a non-steady state response.

Electrical Models

Electrical theory is advantageous for its direct applicability to thermal analysis. The basic definition of heat flow :

$$\text{rate of heat flow} = \left(\begin{array}{c}\text{thermal}\\\text{conductivity}\end{array}\right)\left(\begin{array}{c}\text{temp.}\\\text{gradient}\end{array}\right) \quad ...(2.2)$$

is comparable to the fundamental law of Ohm :

$$\text{electrical current} = \frac{\text{potential difference}}{\text{resistance}} \quad ...(2.3)$$

Consequently, heat flow is analogous to current, conductivity to the inverse of the resistance and the temperature gradient to the potential difference (Dainty, 1960).

Taking into consideration the capacity of the body to store heat, heat loss may be represented by a simple series R-C circuit, as shown in Fig. 2.10. The assumption that is necessary to make such a simple model valid, is that the initial skin temperature, To, is set to a predetermined value. The temperature gradient can then be estimated, after the alteration of the thermal load. The supply voltage in the model would therefore represent the thermal load to the body and the time constant of the capacitative element would be related to some physical traits of the human body, determining its ability to store and lose heat.

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Machle and Hatch (1947) and MacDonald and Wyndham (1950), having followed a similar approach, derived the following relationship :

$$Ts = T2 - (T2-T1) \exp(-((SA \times K)/(c \times b))t) \qquad ...(2.6)$$

where,

T1, T2 = initial and final steady state skin temperatures, before and after the alteration of the heat load

SA x K = product of body surface area and equivalent thermal conductance to air, K, which combines heat loss due to radiation, convection and evaporation

c x b = product of total body heat capacity and the weighting factor of deep and surface body temperature.

In order to accommodate for the production of heat within the body, a heat generating component must be added to the model depicted in Fig. 2.10. MacDonald and Wyndham (1950) proposed a model as depicted in Fig 2.11, whereby the heat production is simulated by a current generator. This model is further improved by discerning between thermal capacity of the core, Cr, and the skin, Cs, and also by accounting for the resistance between core and skin, Kint, as seen in Fig. 2.11. An improvement to the model is the introduction of a rectal and peripheral feedback loop.

Fig. 2.10 : Electrical engineering analog of the
thermoregulatory system. From MacDonald and Wyndham (1950).

71 a
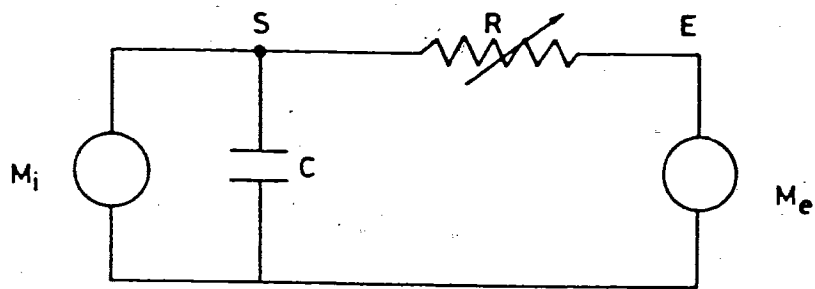
Fig. 2.11 : Electrical engineering thermoregulatory model with a feedback loop. MacDonald and Wyndham (1950).
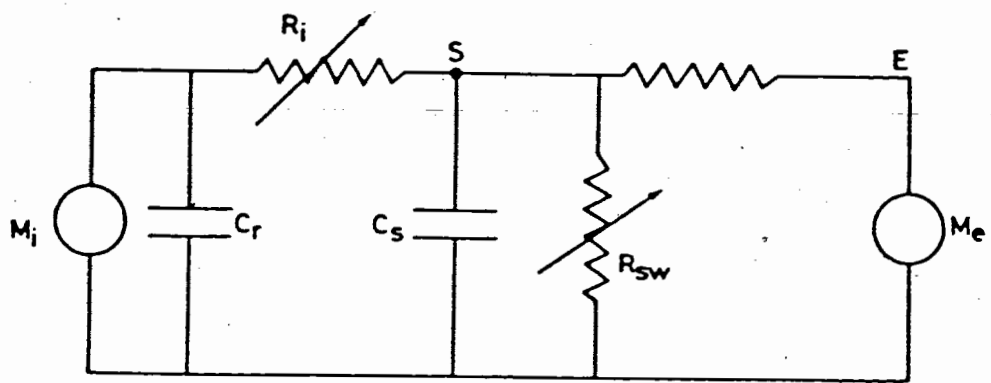
As more factors are taken into consideration, the complexity of electric analogues increases. Riggs (1976), included heat loss due to evaporation and respiration, by including two respective current generators.

The above models may be popular, due to the ability of translating most electrical parameters into physiological terms. However, the complexity of the thermoregulatory system does not allow adequate simulation with such simple electrical circuits.

These models also do not model the thermogenic response, but attempt to describe mainly the maintenance of thermal balance in the human body.

Thermodynamic Models

Wissler (1961) developed one of the first concise models of thermoregulation, based on thermodynamic principles. His original model, separating the body into six segments, was modified (Wissler, 1970) to an analysis of fifteen compartments (Fig. 2.12). His model includes consideration of distribution of metabolic heat generation, conduction of heat within tissue, convective transfer of heat by flowing blood, loss of heat by radiation, convection and evaporation at the skin surface, respiratory heat loss, counter-current heat exchange, geometry of the body, relatively low thermal conductivities of the superficial layers of fat and skin and environmental conditions.

Fig. 2.12 : Components used in the construction of a
    mathematical model of the human thermal system based upon 15
    elements connected by the circulatory system. From Wissler
    (1964).

Q_r

74b
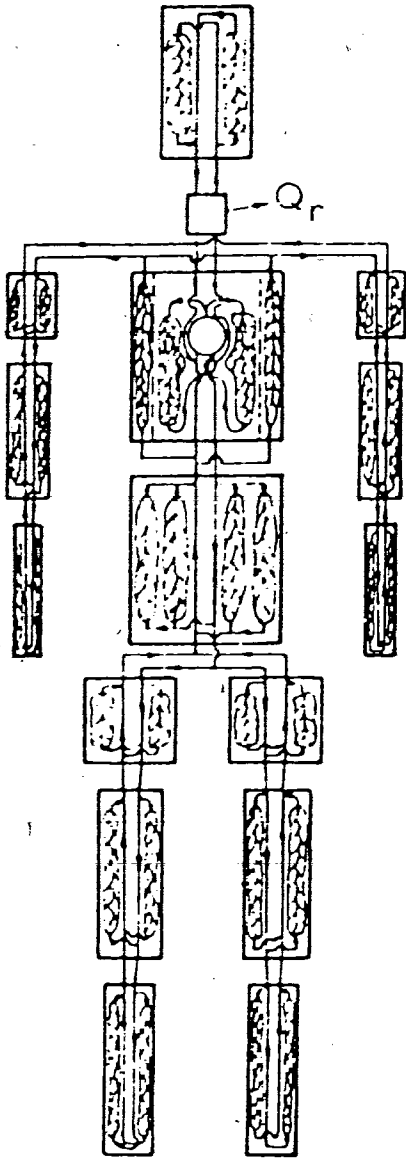
The model applies to a uniform longitudinal framework of cylinders and is affected by the position of the body. As Wissler points out, whether a subject is curled up in a ball or stretched out will affect the relative heat loss. This has been confirmed in cold water experiments by Hayward et al. (1975b). The posture and position of an individual will also affect the convective heat loss, be it in air or water, as the surface exposed to the ambient is reduced (Kerslake and Waddell, 1958). Wissler's model does not accurately portray the multilayer structure of the 15 segments, which may result in inadequate evaluation of heat transfer from core to periphery and heat loss by convection from the skin to the surrounding environment. Boutelier et al. (1977) have shown that the magnitude of the heat transfer coefficient in humans, quantifying the amount of convective heat loss from the skin to the ambient, is inversely related to the skinfold thickness. Also, the model assumes a constant mass of blood throughout the exposure to cold. Although the change in blood volume due to cold exposure is slight, there is definitely a redistribution of blood within the body. This implies that in a segmental analysis, the volume of blood within a specific compartment will change with time and upon immersion (Arborelius et al., 1972). In air, a similar problem may be encountered during postural changes. In the supine position, the volume of blood will decrease in the extremities and will accumulate in the lungs (West, 1978).

Wissler suggests, that one of the main downfalls of his model is the neglect of longitudinal heat loss from the head. Although this may be insignificant in the limbs, it is quite substantial in the head. Nevins and Darvish (1970) proposed a heat transfer model for the head, by assuming the head to be a sphere, as opposed to a cylinder as suggested by Wissler. Their method of solution considers a multilayer structure and accounts for heat generated in each layer of tissue.

The model developed by Wissler primarily solves the heat balance equation for the body and evaluates the heat content of the body, and heat transfer within the body and at the boundary of skin-to-ambient. To calculate the amount of thermal energy generated by shivering thermogenesis, Wissler uses the predictive equation of Hayward et al. (1977) relating metabolic rate with skin and core temperature.

Analogue Computer Models

The application of analogue computers made it possible to generate complex functions necessary to simulate the control mechanisms involved in thermal homeostasis. Wyndham and Atkins (1960) improved their initial R-C circuit model with a concentric cylinder model, shown in Fig. 2.13. This model incorporates various layers of the body and enables the establishment of neural control of thermoregulatory processes. The model has been complemented by Stolwijk and Hardy (1966)

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Fig. 2.13 : Concentric cylinder model. From Atkins and Wyndham (1969).

OUTER SKIN
SKIN AND TISSUE
MUSCLE
CORE

vascular convection

heart lungs T_a

radiation T_r

T_s convection T_{air}

wind V.

evaporation P_a

P_s V.

blood flow

heat production

sweat rate

T

T_s

CONTROL
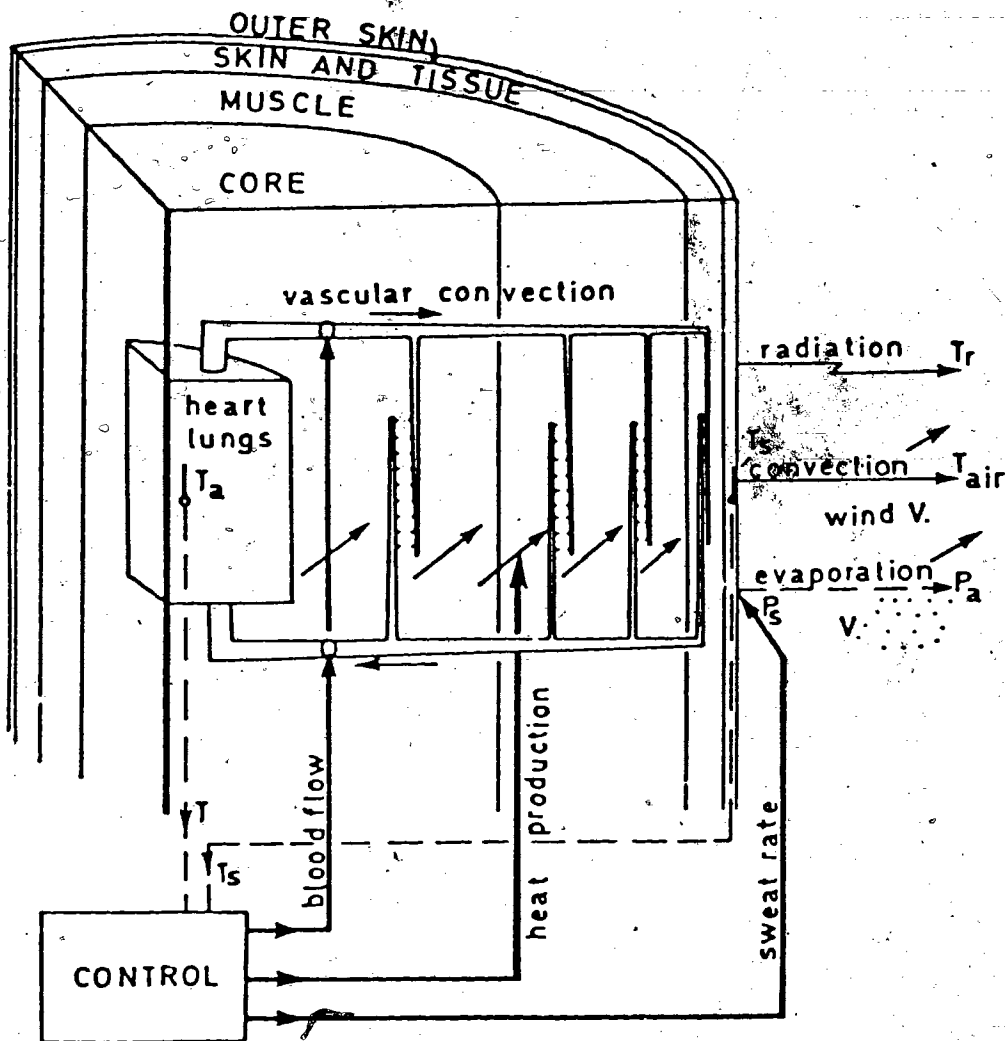
whose model involves segmental analysis of heat loss in the body and takes into account the counter-current heat exchange between arteries and veins. Wyndham and Atkins include this vascular heat exchange within the core in their modified version of the concentric cylinder model. Their model only represents a unique solution to the problem and not an optimal one. It offers an adequate analysis of heat flow through several layers of the body and heat loss from the skin, but does not include consideration of respiratory heat loss, for example.

Consideration of the various factors involved in cold water immersion enabled Montgommery (1974a) to construct a comprehensive thermal analogue computer model for SCUBA divers. The model differs from other models mainly in its consideration of the thermal protection offered by the diving suit. Although the effects of increased ambient pressure on the central nervous system of animals and man are well documented (Brauer, 1975; Bennett, 1976), the effects on the thermoregulatory control system have as yet not been reported.

Computer Models

Computer models have allowed the mathematical models to become of practical use in predicting cooling rate and responses to thermal stress. At one stage, the complexity of thermodynamic models outgrew the bounds of practicality, while trying to achieve improved accuracy. The use of on-line digital computers

has regained the applicability of mathematical simulations.

Most of the previously mentioned models have been transcribed in some modified form into digital computer models. Recent contributions in this field have been made by Stolwijk (1970, 1971) and Montgommery (1974a). They both establish equations of heat balance from basic thermodynamic principles and also consider neural control of thermoregulation. Their models take into account the subcutaneous tissue, as well as the muscle layer within the segments of the body.

Of particular interest is the model developed by Montgommery (1974a,b), as its concern for thermal homeostasis in divers makes it applicable to immersion situations. Based on similar principles adopted by Stolwijk and Hardy (1966), it also accounts for the ambient pressure as well as thermal conductivity, heat capacity and density of water. The analysis of respiratory heat exchange considers the pressure and specific heat of the inspired gas. Heat loss by evaporation will depend on a combination of ambient pressure or depth of the diver and gas mixture used.

The model derived by Montgommery (1974a,b) recognizes that one of the more prominent heat loss sites in the body is the respiratory tract. Unfortunately, the models of Stolwijk and Hardy (1966), Stolwijk (1970, 1971) and Montgommery (1974a,b) assume values for the average man and are inaccurate for people with too large or too small subcutaneous adipose tissue deposits.

Neuronal Models

Neural models allow the information discussed in the earlier section on neurophysiological thermoregulation, to be presented schematically. Models can clearly map out excitatory and inhibitory pathways and suggest possible effector mechanisms.

The activity of cold and warm sensors has already been presented in Fig 2.1. It indicates, that at thermoneutral temperatures, activity of thermosensors is identical for both cold and warm sensors and the resultant thermoregulatory drive is at its minimum; a region defined as the set-point temperature. Cooling and heating however, will elicit different patterns of activity from these sensors, as seen in Fig. 2.2.

From speculations of Bazett (1949) and Vendrik (1959), Bligh (1973) proposed a model depicted in Fig 2.14. The warm and cold sensors having similar stimulus characteristics, only in opposite direction. Neural drives from the sensors are inhibited by a constant activity/temperature drive from interneurones, displacing the response pattern generated by the sensors. The natures of the stimulus determines the effector mechanisms whether they are heat loss or heat production by nature. The assumption that temperature insensitive interneurones play an integral role in thermoregulation, specifically in the determination of the set-point temperature, is speculative. The

Fig. 2.14 : A sustained inhibitory influence acting on both thé warm sensor to heat loss pathway and on the cold sensor to heat production effector pathway. The central graphs represent the combined activity(A)/temperature(T) patterns of the peripheral warm and cold sensors and the subsequent interneurons. The activity in the pathways to heat loss (HL) and heat production (HP) effectors is zero at what amounts to a set-point temperature (Tset). The activity along the pathway to heat loss effectors increases as core temperature rises above this set point, and that to heat production effectors increases as core temperature falls below this set point. From Bligh (1973).

Warm —o ————— ⟨·o ————————————→ Heat loss(HL)

Cold —o ————— ⟨·o ————————————→ Heat production(HP)

A

T

HP   HL

T_{set}

81b
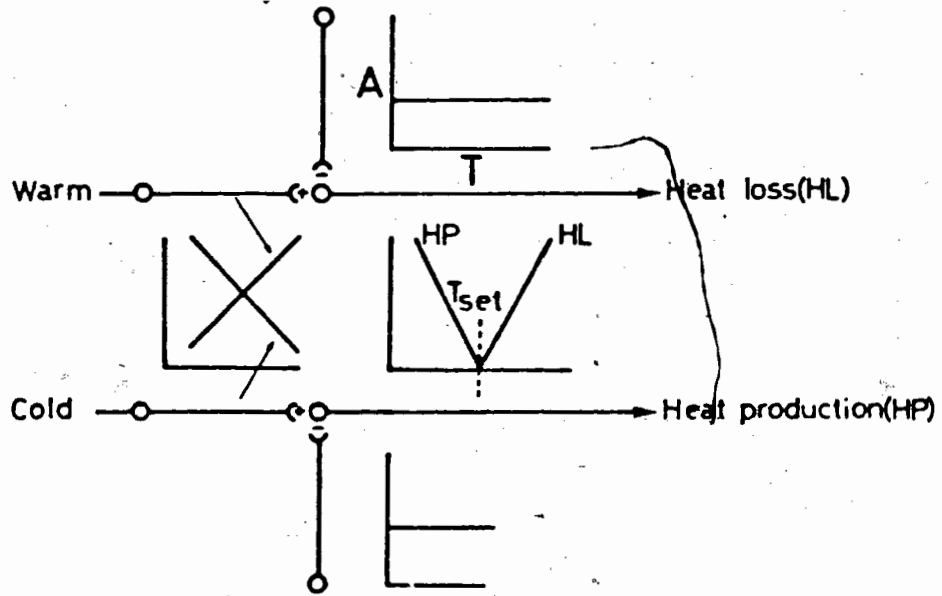
set-point temperature is already established by the primary

thermoreceptors, by their static response characteristics.

It has been observed, that body temperature may be

regulated at higher or lower temperatures, than the set point

temperature. Examples of this are during sleep, when core

temperature drops (Webb and Hiestand, 1975; Buguet et al.,

1979), exercise (Brengelmann, 1977) and fever (Mellon, 1975,

Stitt, 1981), when core temperature is maintained at higher

levels. Such observations led Hammel et al. (1963) to propose a

hypothesis, that the set point temperature is not constant, but

may be adjusted. The adjustable set-point theory, shown

diagramatically in Fig. 2.15 (Bligh, 1972), explains how a

thermoregulatory response as a result of a certain level of core

temperature, may vary depending on the level of the set-point

temperature. Fig. 2.15 also outlines several known mechanisms,

which either raise or reduce the level of the hypothetical

set-point temperature.

To include hypothalamic thermosensitivity and reciprocal

inhibition of neural drive from temperature sensors, Wyndham and

Atkins (1968) suggested an arrangement in Fig. 2.16. The

proposed inhibition of heat loss mechanisms from hypothalamic

cold receptors, has not yet been validated. The model also

neglects to consider the role of the spinal cord in

thermosensitivity and as an extrahypothalamic integrative

centre.

Fig. 2.15 : A schematic representation of the theory of an
   adjustable set point. Thermoregulatory responses are
   controlled by, and are proportional to, the difference
   between the set point and the hypothalamic temperature (T_{set}
   - T_{hyp}.). Afferent neural influences emanating from
   extra-hypothalamic temperature sensors and higher centres,
   act on the set point either raising (+) or lowering (-) it.
   Adapted from Hammel, 1964 (also in Bligh, 1973).

afferent influences

peripheral cold receptors $+$

extra-hypothalamic cold receptors $+$

pyrogens $+$

muscle (exercise) $\pm$?

peripheral and extra-hypothalamic warm receptors $-$

sleep or eyes closed $-$

pain $-$

raise T_{set}

$(+)$

T_{set}

$(-)$

lower T_{set}

$T_{set} - T_{hyp.}$

39° C.

38°

37°

36° $T_{hyp.}$

35°

thermoregulatory responses proportional to $(T_{set} - T_{hyp.})$

$T_{set} > T_{hyp.}$:
peripheral vasoconstriction, shivering

$T_{set} < T_{hyp.}$:
peripheral vasodilatation, sweating or panting

83b
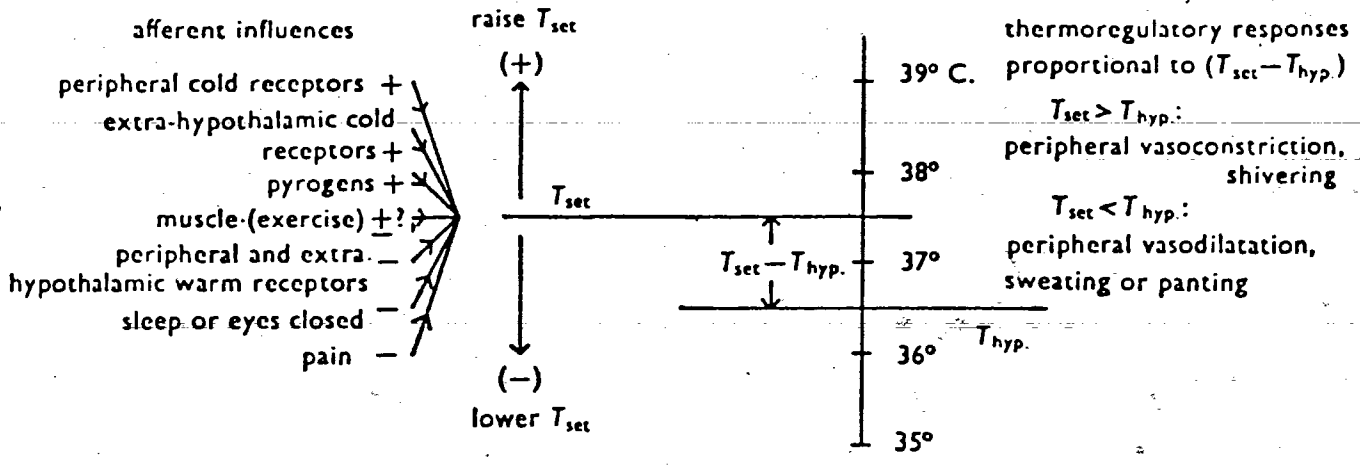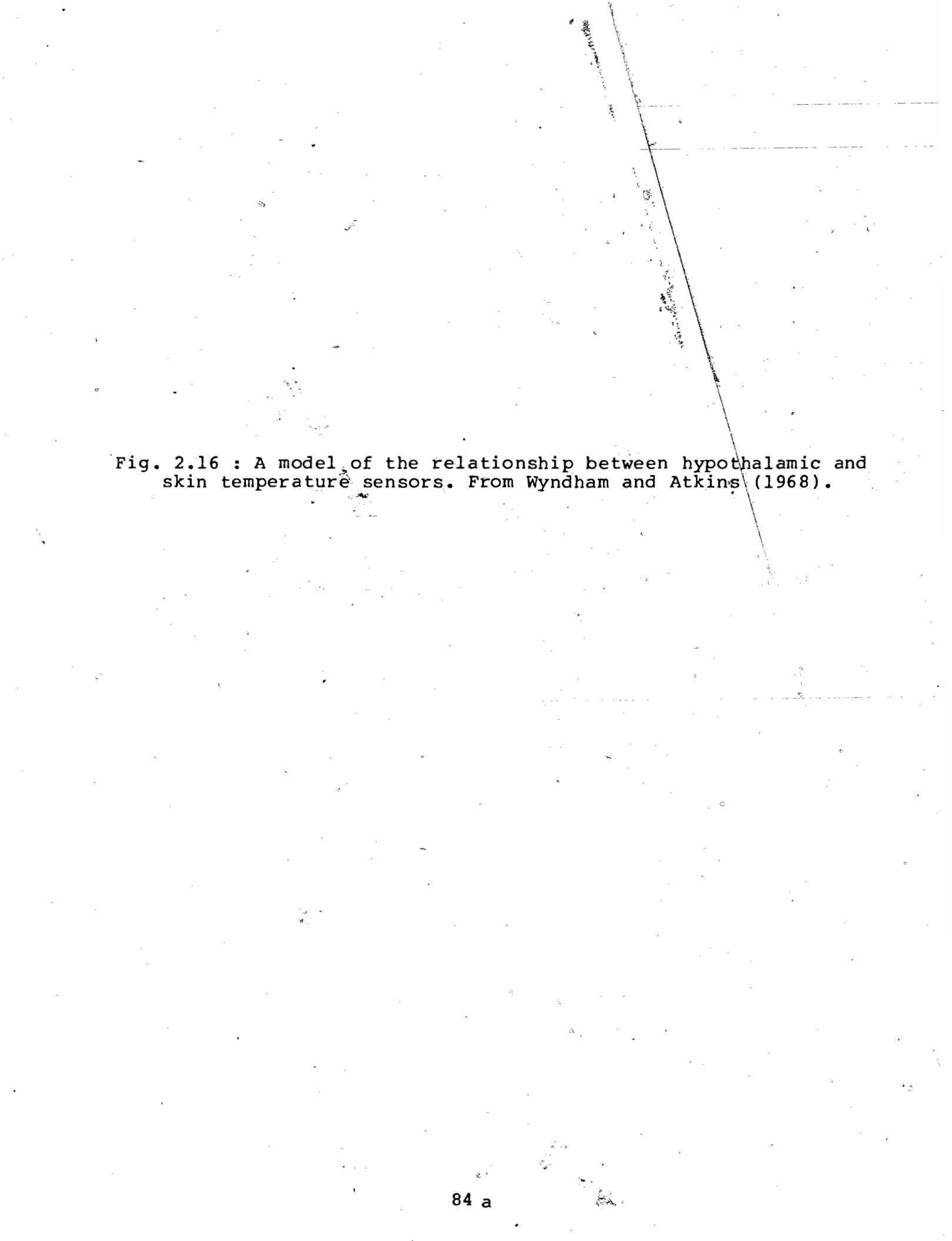
Fig. 2.16 : A model of the relationship between hypothalamic and skin temperature sensors. From Wyndham and Atkins (1968).

Hypothalmic Receptors

Cold   Hot

HEAT CONSERVATION   HEAT LOSS

Integrating centre   Integrating centre

Cold   Hot

Skin Receptors

84b
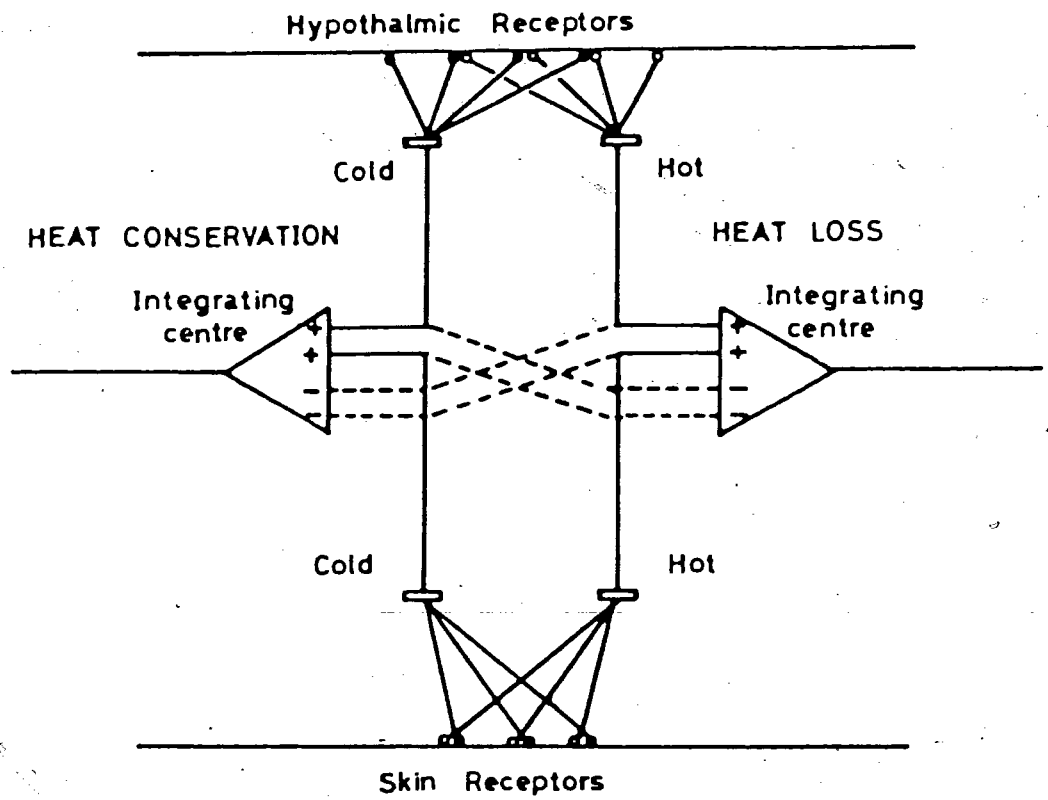
Nakayama et al. (1963) observed two distinct forms of thermoresponsiveness of neurons in the pre-optic anterior hypothalamus; some increased their firing acitivty quite dramatically with increases in local temperature, while the majority of the neurons exhibited very small changes in firing rate in response to local temperature changes. These thermosensitive units have been termed 'high Q10' and 'low Q10' units, respectively, on the basis of their thermoresponsiveness. Hammel (1965) suggested that the set-point temperature is established by an interaction of these 'high Q10' and 'low Q10' units in the pre-optic anterior hypothalamus. The level of the set-point being the region where the firing rate of the two types of units is identical; this occurs at the point where the activity/temperature lines of these units transect (Fig. 2.17).

Changes observed in thermoregulatory responses as a result of adaptation, or acclimatization, have prompted Hensel (1982) to suggest an adaptive component in neural models, as seen in Fig. 2.18 . It is suggested that adaptive changes occur centrally (Bruck and Hinckel, 1982), thereby modifying thermoregulatory responses to peripheral thermal stimulation. The nature of these adaptive components have only become apparent through recent studies investigating the involvement of the lower brain stem in the thermoregulatory control system (Hinckel et al., 1983b) and its inhibitory effect on shivering, modulated after cold adaptation (Hinckel and Schroder-Rosenstock, 1982; Hinckel et al., 1983a). These studies

Fig. 2.17 : The set point temperature as determined by the thermal responsiveness of 'high Q10' and 'low Q10' units in the POAH. From Hammel (1965).

NEUTRAL TEMPERATURE

High Q_{10}

T_{set}

Low Q_{10}

COLD

T_{set}

WARM

T_{set}

ACTIVITY (Firing rate)

35   39   43

HYPOTHALAMIC TEMP ($^\circ$C)
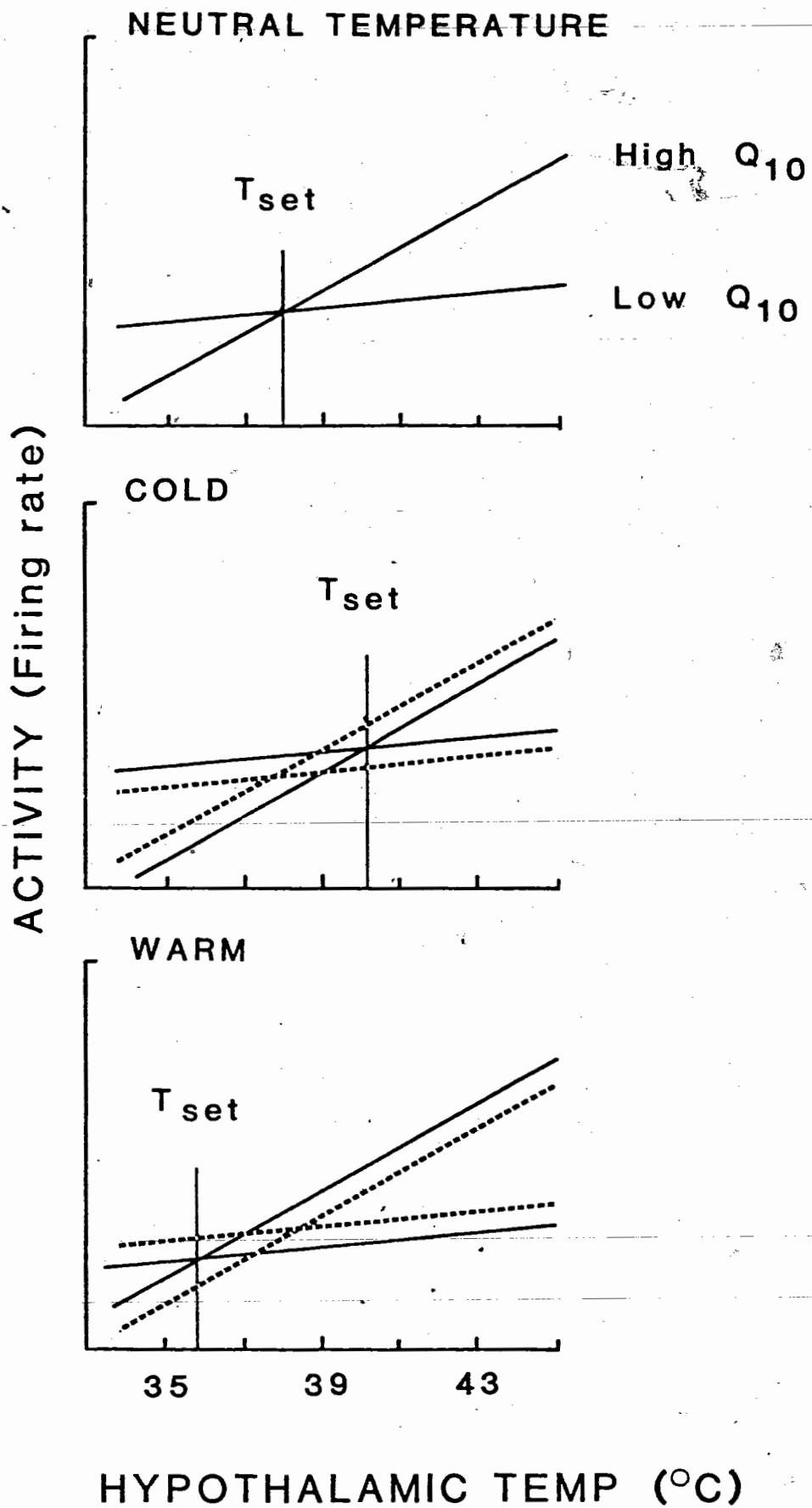
Fig. 2.18 : Adaptive modifications of the thermal control
system. From Hensel (1982).

Chronic or repeated inflow
CENTRAL NERVOUS SYSTEM
Endocrine System
Afferent impulses
Direct action
Efferent impulses
Hormonal control
SENSORS
ADAPTIVE CHANGES
EFFECTORS
Regulatory system
Capacity of effectors
Heat production
Insulation
Evaporation
Skin sensors
Core sensors
CONTROLLED CORE TEMPERATURE
CHRONIC STRESSOR
Thermal environment
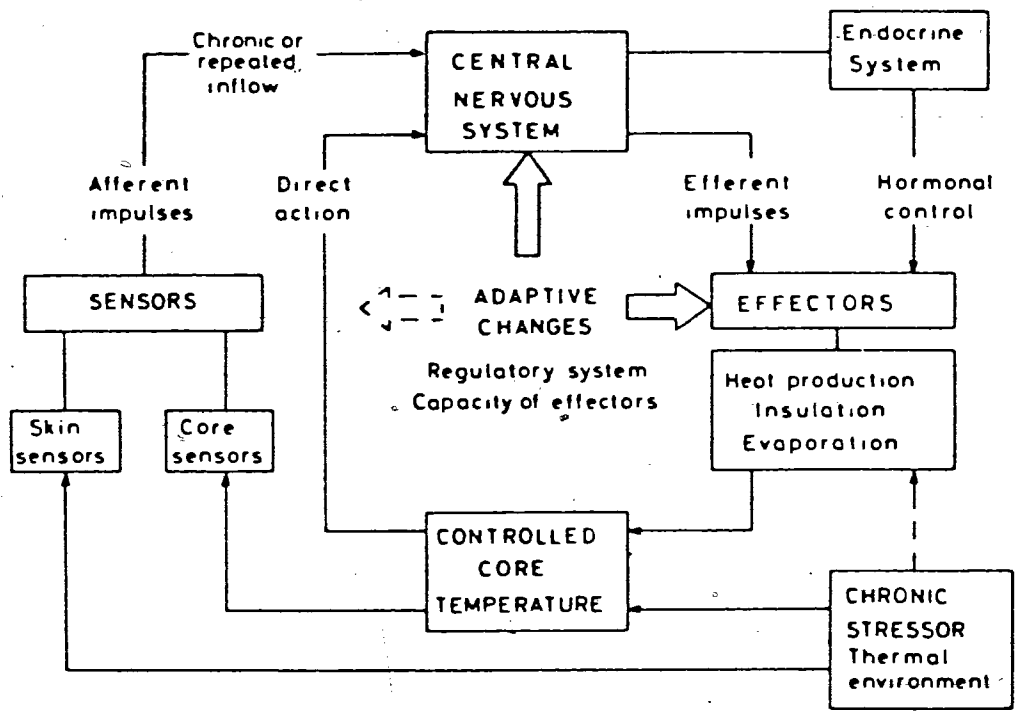
demonstrated that peak firing rates of cold sensitive neurons in the subcoeruleus region of the lower brain stem in guinea pigs, responding to cutaneous thermal stimulation, were substantially reduced after a five week cold adaptation period. Their findings suggest this to be a possible explanation for the decrease in shivering threshold temperature, due to prolonged cold exposure, observed in man and animals. Similar adaptive modifications have been reported in warm responsive neurones in rats (Werner et al., 1980).

Bruck and Hinckel (1982) suggest that central cold adaptation may be either long-term or short-term in nature. The reductions in average static peak firing rates due to five week adaptations at $5^{O}C$, as seen in cold sensitive neurones in the subcoeruleus region of guinea pigs by Hinckel and Schroder-Rosenstock (1982), is attributable to long-term adaptation. The cold sensitive neurons in the subcoeruleus region also exhibited short-term modifications in response to persistent cutaneous thermal stimulation (Bruck and Hinckel, 1982). The time course for this short-term component was in the order of several minutes, thus separating the effect from the dynamic responsiveness of peripheral thermoreceptors, having a time constant of several seconds (Kenshalo and Duclaux, 1976). In contrast to the cold afferent role of the subcoeruleus region of the brain stem, the nucleus raphe magnus has been observed to elicit inhibition of shivering thermogenesis. Hinckel et al. (1983a,b) have demonstrated that electrical stimulation of the

nucleus raphe magnus causes marked decreases in oxygen consumption, electrical muscle activity and body temperature, during cooling of guinea pigs in a climatic chamber.

The involvement of the lower brainstem in the mediation of shivering inhibition (Hinckel et al., 1983a,b) and cold adaptation, has recently been incorporated in a neuronal model, developed by Bruck and Hinckel (1982), depicted in Fig. 2.19. Their model suggests that heat production responses (HP) are a result of not only peripheral cold excitation (CR), but also peripheral warm inhibition (WR). Conversely, heat dissipation (HD) is dependent on peripheral warm (WR) and cold receptor (CR) stimulation.

Most of the models presented, suggest possible interactive mechanisms, based on static thermoreceptor activity and subsequent effector mechanisms. The role of dynamic activity of thermosensitive structures has not yet been thoroughly investigated. The contribution of dynamic activity to the magnitude and latency of various thermoregulatory effectors remains to be identified.

Fig. 2.19 : Tentative connectivity model of thermoafferent
systems with special reference to the recently described
thermoregulatory monoaminergic brain stem pathways, mainly
originating in two lower brain stem centers. Trunk skin warm
receptors (WR) have been shown to project to 5-HT nucleus
raphe magnus (NRM) cells. Projections from NRM ascend to the
integrative hypothalamic networks controlling heat
production (HP; left IN) and heat dissipation (HD; right IN)
and descend to the dorsal horn (DH). The scrotal pathway
takes a special route ascending via the NRM and two medial
midbrain structures, the nucleus raphe dorsalis (NRD) and
the adjacent central grey matter (CG), partly to the
hypothalamus and partly to the thalamus and sensory cortex.
In the figure, NA denotes noradrenergic projections, IN the
integrative interneuronal mechanisms, EN the effector
network and CR the skin cold receptors. Adapted from Bruck
and Hinckel (1982).

90b
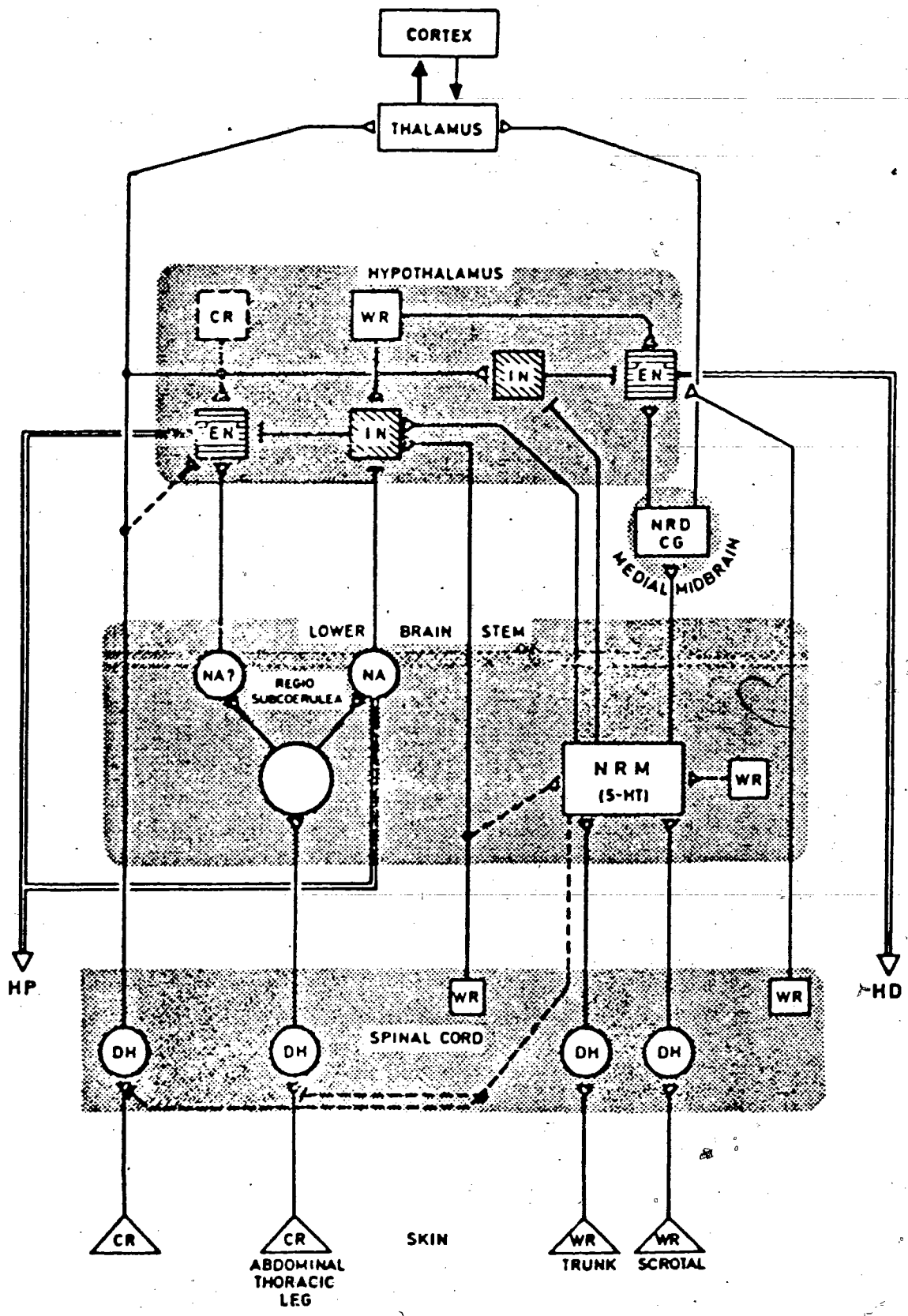
V. References

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C. EVALUATION OF PREDICTIVE FORMULAE FOR DETERMINING METABOLIC RATE DURING COLD WATER IMMERSION

I. Introduction

Although interest in the existence of internal temperature in mammals stems back as far as the Greek philosophers, most notably Plato (Cornford, 1957) and Aristotle (Peck, 1943), the major breakthrough in the theory of thermal homeostasis was achieved by Lavoisier (1777 a,b), who developed the oxidation theory of combustion. Lavoisier implicated the oxidation theory in the thermogenic process in the mammalian body. Specifically, he found that metabolic heat production was directly related to the consumption of oxygen and production of carbon dioxide. With this concept, Lavoisier offered researchers in thermal homeostasis a quantitative method of assessing heat production or energy expenditure in the human body (see Mendelsohn, 1964; for historical review). Since the pioneering experiments of Lavoisier and Laplace (1780), researchers have been attempting to establish a mathematical description of the thermoregulatory system. The mathematical models developed are based on fundamental thermodynamic principles and range from simple models (Burton, 1934) to more complex versions (Atkins, 1962; Wissler, 1964; Hsu, 1971), with the advent of electronic computers.

Unfortunately, in most mathematical models the human body has been modified to suit the standard thermodynamic laws. The basic assumptions of some models, implying that the human body consists of symmetrical cylinders and spheres, whose organs

function in a very uniform manner, gives rise to substantial errors. Such complaints of taking analogies in human thermal homeostasis too far have already been echoed by Stevenson (1771) two centuries ago, when he proclaimed :

> "Not content with the ingenious and useful Application of Levers, Ropes and Pulleys; to the Bones, Muscles and Tendons, and other valuable mechanical and hydrostatical Pursuits : Not content with these, I say, Millstones were brought into the Stomach, Flint and Steel into the Blood-vessels, Hammer and Vice into the Lungs, &c. But all to no good Purpose; there being certain Bounds which mechanical Principles and Demonstrations do not reach."

Several attempts have been made to derive relationships for predicting the response of the human thermoregulatory system to various thermal stimuli (Stolwijk and Hardy, 1966; Brown and Brengelmann, 1970; Nadel et al., 1970; Hayward et al., 1975, 1977). These predictive formulae based on empirical data, although reported to be representative of the thermoregulatory control system in the body, have varying degrees of predictive power. Most formulae share a similar belief in the existence of a set point temperature and the hypothetical relationship proposed by Benzinger (1969), namely that metabolic rate is a function of steady state core and skin temperature. Benzinger proposed that the metabolic rate is directly related to the tympanic temperature with respect to a certain "set-point" and the skin temperature. Benzinger's experimental results based on one subject have been widely accepted and have become textbook examples of the thermoregulatory system in humans. Benzinger's experiments, presented in a review (1969), have not been repeatable (Craig and Dvorak, 1966) and have only on occasion

been challenged (Brengelmann, 1967). Upon observing such discrepancies in the literature, as in the case of the results of Benzinger (1969) and of Craig and Dvorak (1966), one is compelled to argue over the validity of the results and experimental procedure of the respective investigators. However, from a control systems aspect, both results support the hypothesis, that the metabolic rate is a function of internal and surface skin temperature.

One of the problems associated with the hypothetical relationships proposed by Benzinger, is that his "steady-state" core and skin temperatures had a slight gradient. Coupled with the later findings of Craig and Dvorak (1966), this tends to suggest that metabolic rate is dependent upon not only the "steady-state" body temperatures, but also on the dynamic changes in core and skin temperatures, that occur during cooling. Perhaps the discrepancies in the skin isotherms of Benzinger and Craig and Dvorak occurred due to different rates of cooling of the body temperatures. Such an hypothesis is certainly supported by studies of isolated temperature sensitive neurons (Hensel and Boman, 1960), which have indicated the presence of a powerful dynamic response to a temperature change. If this is the case, then relationships suggesting that metabolic rate at a given combination of core and skin temperatures will be the same, regardless of the rate at which the core and skin temperatures are changing, are not valid. It seems unfortunate, that latter predictive expressions for

metabolic rate have omitted modifying Benzinger's relationships to include dynamic components and have continued to define metabolic rate (MR) as a function of steady state rectal (Tr), tympanic (Tty) and skin (Ts) temperature.

The concept of dynamic components in the control of metabolic rate is not new and has been suggested by Brown and Brengelmann (1970), Nadel et al. (1970) and Morrison et al. (1980). Assuming therefore, that there exists a relevant contribution of dynamic as well as static core and mean skin temperature to the control of thermogenic processes in the human body, existing static formulae could be modified to include components of dTs/dt and dTr/dt or dTty/dt and thereby improve their overall predictive power for cooling and rewarming. The modified formulae would then reflect the apparent hysteresis that occurs when plotting metabolic rate against core or skin temperature during cooling and rewarming, and thereby express metabolic rate during these two phases with more validity.

This chapter evaluates several predictive formulae. It examines the predictive power of these expressions, the regions where error occurs, and identifies any consistent discrepancies between theory and experiment by analysis of errors. Finally, it offers several possible methods of minimizing the error of prediction of these formulas.

II. Method

The empirical data used to evaluate models which predict the metabolic response to a cold exposure, was obtained from a study conducted by Morrison et al. (1982). The protocol used in their study, which consisted of cooling ten male subjects in 10^OC water until a rectal temperature of 35^OC was reached, followed by passive rewarming in a sleeping bag, has been outlined previously by Morrison et al. (1979) and Conn (1980).

Metabolic heat production was calculated as outlined by Consolazio et al. (1951; also see Appendix I.). Oxygen consumption values, corrected for body mass (i.e. ml. O2/min./kg.) were converted into units of Watts/kg., assuming the calorific equivalent for one liter of oxygen to be 4.8 kilocalories and 1 kcal/hour to be equal to 1.1622 Watts (see Appendix I. for conversion details).

The models of thermogenesis chosen for evaluation were :
1. Hayward et al. (1977), H1 :

$$MR(W/kg.) = 0.0314 (Ts - 42.4) (Tr - 41.4) \quad ...(3.1)$$

H2 :

$$MR(W/kg.) = 0.0356 (Ts - 41.8) (Tty - 41.0) \quad ...(3.2)$$

2. Stolwijk and Hardy (1966), SH :

$$\Delta MR(kcal./hr.) = 60 \ (36.6 - Tty) \ (34.1 - Ts) \quad \ldots(3.3)$$

3. Nadel et al. (1970), N :

$$\Delta MR(kcal./hr.) = 36 \ (36.5 - Tty) \ (32.2 - Ts) +$$
$$+ \ 7 \ (32.2 - Ts) \quad \ldots(3.4)$$

4. Timbal et al. (1976 a,b), T :

$$MR(W/m^2.) = 41.31 - 57.77 \ (dTs/dt) -$$
$$- \ 5.01 \ (Ts - 34.0) +$$
$$+ \ (894.15 - 23.79 \ Tr) \quad \ldots(3.5)$$

5. Brown and Brengelmann (1970), B :

$$MR = J \ (Ts + K \ (dTs/dt)) - L \ (dMR/dt) \quad \ldots(3.6)$$

where,

H1,H2,SH,N,T,B, = notations to denote the specific model.

MR = metabolic rate

Ts = weighted mean skin temperature

Tty = tympanic temperature

Tr = rectal temperature

J,K,L = undetermined coefficients

In order to be able to draw comparisons between the predictions of the above models and observed values, predicted and observed metabolic rates were converted to units of Watts/kg.

The analysis was confounded by different experimental techniques employed by the authors in obtaining measures of core and peripheral temperatures, from which various linear and multiple linear regression analyses were conducted in order to obtain the parameters in the models. Measurement of oxygen consumption is a fairly standard procedure and it is assumed that the metabolic rates determined by the authors are comparable.

The evaluation of core temperature was achieved by measuring the temperature in the rectum and at the tympanum. As can be seen from Table 3.1, probe placement in the rectum varied from 10 cm. to 15 cm. beyond the anal sphincters. The change in rectal temperature with depth of insertion has been reported by Behnke and Yaglou (1951), who observed differences of up to $0.5^{o}C$ between depths of 5 cm. and 9 cm. Mead and Bonmarito (1949) observed similar differences in one subject between depths of 7.5 and 12.5 cms. (a comparative evaluation of core temperature readings taken at different sites is given in Appendix IV). The data from both reports suggests that the rate of cooling remains the same regardless of the depths investigated, thereby maintaining the difference constant.

Table 3.1 : Techniques employed in several studies for measuring
core and peripheral temperature.

Study	Skin temperature	Core temperature
Present study	Measured at four sites: arm,chest,thigh,calf $Tskin=0.3(Tarm+Tchest)+0.2(Tthigh+Tcalf)$	Rectal: 15cm. beyond the anus Tympanic: at the tympanum
Hayward et al. (1977)	Measured at two sites : arm and chest $Tskin = 0.5(Tarm + Tchest)$	Rectal: 15cm. beyond the anus Tymapnic: at the tympanum
Stolwijk and Hardy (1966)	Measured at three sites: trunk,head,extremity $Tskin = 0.37(Ttrunk) + 0.9(Thead) + +0.54(Textremity)$	Rectal* Tympanic * Extremity (only suggested)
Nadel et. al. (1970)	Not reported	Rectal * Tympanic *
Timbal et al. (1976)	$Tskin=0.07(Tfoot)+0.13(Tcalf)+0.19(Tthigh)+ +0.12(Tabdomen)+0.12(Tchest)+0.12(Tback)+ +0.08(Tupper\ arm)+0.06(Tforearm)+ +0.05(Thand)+0.06(Tforehead)$	Rectal: 15cm. beyond the anus
Brown and Brengel- mann(1970)	$Tskin =$ bath temperature	Rectal: 10cm. beyond the anus Tympanic: at the tympanum

* exact depth of insertion not reported.

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The greatest discrepancy in data collection appears to be the evaluation of mean skin temperature (Table 3.1). A preliminary study revealed that better predictions were obtained using the formula for mean skin temperature as suggested by Ramanathan (1964), utlizing weighted temperatures of the arm, chest, thigh and calf as opposed to the method used by Hayward et al. (1977) and Stolwijk and Hardy (1966). The empirical data from Morrison et al. (1982) and Conn (1980) only contained measurements of skin temperaure at four sites, making it impossible to use the methods suggested by Timbal et al. (1976 a,b). However, Mitchell and Wyndham (1969) have suggested that the formula of Ramanathan (1964) is adequate. For the purposes of the present study, weighted mean skin temperature was evaluated as shown in Table 3.1

The models differ not only in the values of the coefficients, but also in the functional relationship between the dependent and independent variables. Some predict metabolic rate (H1,H2,T), others only provide an estimate of the change in metabolic rate (SH and N). The model suggested by Brown and Brengelmann (1970) will be evaluated separately, as it has not been tested with empirical data and hence they did not report the coefficient values. Therefore, only the functional relationship of the model was tested. The formulae of Timbal et al. (1976 a,b) and Brown and Brengelmann (1970) have in common the consideration of dynamic components. Timbal et al. (1976 a,b) account for the rate of change in skin temperature, while

Brown and Brengelmann (1970) also consider the thermoregulatory system as a closed loop, negative feedback system and also take into consideration the rate of change of metabolic rate.

The aim of the present investigation was to ascertain which relationship would best describe the metabolic response during cooling and rewarming. By doing so, some of the assumptions and limitations set by the authors were not taken into consideration. However, these violations were necessary to allow comparisons and to determine whether the models could be improved, in order to provide accurate predictions regardless of the polarity of the temperature transients within the body.

III. Analysis

The evaluation of the predictive models was conducted in several steps, each utilizing an appropriate statistical procedure. The nature of these statistical analyses and justification for their application are outlined below :

1. Before attempting to evaluate the predictive formulae in any great detail, it was determined whether the proposed relationships were significant, using the empirical data. In other words, is there a valid functional relationship between the dependent variable (observed metabolic rate) and the independent variable (metabolic rate predicted using the mentioned models), The Student's t-test was used to test the null hypothesis that the population correlation coefficient is zero (Roscoe, 1969; Klugh, 1974) :

$$t = r \times (N - 2) / (N - r^2) \qquad \qquad ...(3.7)$$

with degrees of freedom (d.f.) = N-2 .

where,

r = correlation coefficient

N = number of cases

The correlation is deemed significant, if the calculated value of t is equal to or greater than the tabulated value of t with (N-2) degrees of freedom.

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By determining a significant level of t, with (N-2) degrees of freedom, a rejection region for the correlation coefficient may be defined as :

$$r = t^2 / (N - 2 + t^2) \qquad \qquad ..(3.8)$$

with d.f. = N-2

A one-tailed test was conducted, since the a priori specification was that only positive correlations are of interest.

Conducting this analysis on the pooled data (for cooling and rewarming) for ten subjects, it was found that a significant level of t (at 0.05 level for d.f.=230) is 1.645. In order for a correlation to be significant, it has to be equal to or greater than 0.109 (0.183 for cooling only and 0.149 for rewarming only). The coefficient of correlation, r-squared, was adjusted for the number of predictive variables according to Dixon and Jennrich (1981), such that :

$$\text{adjusted } r^2 = r^2 - p(1 - r^2)/(N - p')$$

$$...(3.9)$$

where,

p = number of independent variables

p' = p when intercept is equal to 0 and p'=p+1, if

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intercept is not zero.

Having confirmed whether the proposed equations predict the trend of the empirical data, the validity of their predictions can be quantified from the magnitude of the errors generated, using a least squares regression analysis.

2. The models used to evaluate metabolic rate during the process of cooling and rewarming were considered in a general matrix form :

$$\hat{Y}0 = X \beta \qquad \ldots(3.10)$$

where,

$\hat{Y}0$ = (N x 1) vector of predicted values.

 X = (N x p) vector of known variables. In model H1 the known variables are Ts and Tr.

β = (p x 1) vector of coefficients.

The observed values of metabolic rate, Yi, were compared to the predicted values, $\hat{Y}0$, by:

$$Yi = X \beta + E = \hat{Y}0 + E \qquad \ldots(3.11)$$

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where,

Yi = (N x 1) vector of observed metabolic rates.

E = (N x 1) vector of errors.

A model is therefore said to be accurate, if the sum of the errors generated by the model are negligible, or :

$$\sum_{i=1}^{N} ei \quad \rightarrow \quad 0 \qquad \qquad ...(3.12)$$

The goodness of fit of the models was assessed by testing the individual regression equations, as derived by the statistical computing package Midas (Fox and Guire, 1976). The general form of the regression equations is shown in equation 3.12. To test the statistical significance of the regression, the ratio:

F = (regression mean square) / (residual mean square)

= (MSR) / (MSE)   ...(3.13)

where,

MSR = (sum of squares due to regression) / (d.f. - 1)

= RSS / (ν -1)   ...(3.14)

MSE = (sum of squares due to error) / (d.f. - 2)

= SSR / (ν -2)   ...(3.15)

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is compared as a $F(p-1, \nu, \alpha)$ variate, where ν denotes the degrees of freedom $(N-p)$ and α is the level of significance (0.05). If the value of the mean square ratio exceeds the tabulated value of F, the regression is statistically significant. However, Wetz (1964) proposes the utilization of a "four times" rule, whereby a regression model is termed a satisfactory predictor, if the value of the F ratio exceeds the tabulated value by a factor of four. This was taken into consideration when commenting on the predictive power of the various models. In addition, in order to use the F-test, the following assumptions were made :

a. error of prediction is distributed normally with a variance, σ^2 .

b. variance is constant

c. residuals are independent

3. A better prediction by the same model would involve estimating a new vector of coefficients, β', thus minimizing the sum of the squared residuals, SSR :

$$\sum_{i=1}^{N} e_i^2 = SSR \qquad \qquad \ldots (3.16)$$

For optimum improvement in prediction, a separate vector of coefficients was obtained for individual subjects over three different periods of time; during cooling only, during rewarming only and during the cooling and rewarming period together. This necessitated the redifinition of the vector of coefficients, β, and vector of errors, E, in equations 3.10 and 3.11, respectively. Namely, β becomes a (p x j x k) vector and E a (N x k) vector, where :

j = 1,10 - number of subjects

k = 1 -cooling and rewarming together

    = 2 -for cooling only

    = 3 - for rewarming only.

To determine whether a new β'(at any level of k) has improved the prediction, Fisher's F-test was used to test the null hypothesis :

$$H0 : (Yi - \hat{Y0}) = (Yi - \hat{Y1}) \qquad \ldots(3.17)$$

where,

$\hat{Y0}$ = predictive vector with standard β value.

$\hat{Y1}$ = predictive vector with 'new' β value.

The null hypothesis is rejected , if the ratio

$$(\,(SSR0 - SSR\,)/p\,)/(\,SSR1 / (N - p)\,)\; > F\,(p, N-p, \alpha\,)$$

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where,

SSR0 = residual sum of squares generated by vector $\hat{Y}0$.

SSR1 = residual sum of squares generated by vector $\hat{Y}1$.

4. Models may be improved, in terms of their predictive power, by adding an additional variable in the model. It was suggested in earlier paragraphs that derivatives of peripheral and core temperature should be included in order to improve the prediction. Numerous possibilities exist for modifying the predictive formulae to include dynamic components. Including a dynamic variable as a divisor or multiplier is inadequate, as zero gradients would generate infinite or zero metabolic rates, respectively. The models should predict a change of increased metabolic rate with increasing negative and positive rates of change in peripheral and core temperature. If the derivatives of skin and core temperature are negligible, then the predicted metabolic rate should be a function of the steady state body temperatures.

The method for modifying the models was to add a dynamic component to each steady state variable in the model. The previous standard models were therefore transformed to :

H1 : MRHDT

$$MR = A1 ((Ts - A2) + A3 (dTs/dt)) \times$$

$$\times ((Tr - A4) + A5 (dTr/dt)) \qquad \ldots(3.19)$$

H2 : MRH2DT

$$MR = B1 ((Ts - B2) + B3 (dTs/dt)) \times$$

$$\times ((Tty - B4) + B5 (dTty/dt)) \qquad \ldots(3.20)$$

SH : MRSHDT

$$MR = M0 + C1 ((C2 - Tty) + C3 (dTty/dt)) \times$$

$$\times ((C4 - Ts) + C5 (dTs/dt)) \qquad \ldots(3.21)$$

N : MRNDT

$$MR = M0 + D1 ((D2 - Tty) + D3 (dTy/dt)) \times$$

$$\times ((D4 - Ts) + D5 (dTs/dt)) +$$

$$+ D6 ((D7 - Ts) + D8 (dTs/dt)) \qquad \ldots(3.22)$$

where,

MO = resting metabolic rate.

dTs/dt = rate of change of skin temperature (^{O}C/min.).

dTr/dt = rate of change of rectal temperature (^{O}C/min.).

dTty/dt = rate of change of tympanic temperature (^{O}C/min.).

Ai,Bi,Ci (i=1,5) and Dil (il=1,7) =

= coefficients of regression for models

MRH1DT,MRH2DT, MRSHDT and MRNDT respectively.

An additional parameter in a model implies that a degree of freedom has been lost. To test the significance of the inclusion of additional terms in a model, the following procedure was followed .

The two models were considered in the form :

$$Yi = \hat{Y}1 + E1 = \beta' X + E1 \qquad \qquad \dots(3.23)$$

$$Yi = \hat{Y}2 + E2 = \beta'' X + E2 \qquad \qquad \dots(3.24)$$

where,

β' = vector of coefficients $\beta'i$, where $i = 1,q$.

β'' = vector of coefficients $\beta''i$, where $i = 1,p$.

E1 = vector of errors generated by model $\hat{Y}1$.

E2 = vector of errors generated by model $\hat{Y}2$.

p,q = number of coefficients included in models $\hat{Y}2$ and $\hat{Y}1$, respectively. Note that $p > q$.

The 'extra sum of squares' generated by adding a term to $\hat{Y}1$ as in $\hat{Y}2$, is given by (SSR2-SSR1), where d.f. = p-q.

where,

$$s^2 = SSR2 / (N-p-q) \qquad \qquad \dots(3.25)$$

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Assuming the errors are normally distributed, the ratio:

$$(SSR1-SSR2)/(p-q) \qquad ...(3.26)$$

can be compared with s^2 by an $F(p-q, \alpha)$ test, where:

$$s^2 = SSR2 / (N-P-q) \qquad ...(3.27)$$

where,

SSR1 = sum of the squared residuals generated by $\hat{Y}1$.

SSR2 = sum of the squared residuals generated by $\hat{Y}2$.

The null hypothesis is therefore Ho: SSR2 = SSR1 and the alternative Ha: SSR2 less than SSR1. If the alternative hypothesis is accepted, a significant (at the 0.05 level) minimization of the residuals has been made by adding a term to the equation.

5. In assessing the models, as to which one offers the least amount of error, the equations proposed by Timbal et al. (1976 a,b) and Brown and Brengelmann (1970) should be included. Brown and Brengelmann (1970) did not report preferred values for the coefficients in their model; they were therefore derived using a least squares regression

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analysis.

An F-test was utilized to determine whether the differences between the sums of the squared errors obtained from the various models (H1, H2, SH, TLB, B) were significant at the 0.05 level. This analysis was conducted on pooled data for ten subjects as well as on the pooled cooling and rewarming data separately.

IV. Results

It is evident from Table 3.2, that the correlations for all standard models are significant at the 0.05 level (d.f. = 223), when cooling and rewarming data are treated together. The model suggested by Timbal et al. (1976 a,b) was shown to be poorly correlated with the observed data, when considering the immersion data separately.

When comparing the ratio of (mean squares due to the regression)/(mean squares due to the error) with the tabulated value of F, it was found that the calculated F ratio exceeded the tabulated value in all three time intervals, as seen in Table 3.3.

In order to make a judgement on the usefulness of the equations as predictors of thermogenesis, the 'four times' rule (Wetz, 1964) was applied. The result of this analysis indicates, that all equations are good predictors, when treating the pooled cooling data and rewarming data together. For the cooling data alone, only the models suggested by Hayward et al. (1977) can be considered as adequate predictors of metabolic rate. On rewarming, the equations of Hayward et al. (1977), as well as Nadel et al. (1970) give good predictions of metabolic rate. The overall ranking of the standard models shows that models H1 and H2 are best predictors of metabolic rate.

By using a derivative free non-linear regression analysis (Dixon et al., 1979), the coefficients in the standard equations

Table 3.2 : Significance of correlation coefficients for five
    predictive models.

		Models					Significance level
Condition	H1	H2	SH	N	TLB		
cooling and rewarming	.765	.774	.468	.508	.524	$r \geq .109$
cooling only	.629	.533	.235	.258	.177*	$r \geq .183$
rewarming only	.821	.391	.293	.391	.195	$r \geq .149$

* not significant

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Table 3.3 : Evaluation of standard models with empirical data.

Model	MSR	MSE	F	F_{TAB}	$\dfrac{F}{F_{TAB}}$	Ranking

S : COOLING AND REWARMING DATA

Model	MSR	MSE	F	F_{TAB}	$\frac{F}{F_{TAB}}$	Ranking
H1	872.2	2.724	320.22	3.84	83.39	II.
H2	890.28	2.643	336.88	3.84	87.73	I.
SH	334.32	5.136	65.1	3.84	16.95	V.
N	392.13	4.877	80.41	3.0	26.81	IV.
T	416.77	4.768	87.32	3.0	29.1	III.

C : COOLING DATA

Model	MSR	MSE	F	F_{TAB}	$\frac{F}{F_{TAB}}$	Ranking
H1	153.9	2.826	54.46	3.92	13.89	I.
H2	112.89	3.352	33.68	3.92	8.59	II.
SH	29.58	4.42	6.69	3.92	1.7	*
N	33.78	4.366	7.74	3.07	2.52	*
T	21.08	4.529	4.66	3.07	1.5	*

R : REWARMING DATA

Model	MSR	MSE	F	F_{TAB}	$\frac{F}{F_{TAB}}$	Ranking
H1	580.38	2.137	271.63	3.92	69.29	I.
H2	159.49	5.08	31.4	3.92	8.01	II.
SH	86.3	5.592	15.43	3.92	3.94	*
N	96.98	5.517	17.58	3.92	4.48	III.
T	22.87	6.035	3.79	3.92	0.97	

* Poor predictive power, as determined by $(F/F_{TAB}) > 4.0$ (Wetz, 1964). See text for details.
F and F_{TAB} denote the calculated and tabulated value of the F statistic, respectively.

were altered to give the best possible prediction for each subject. As can be seen from Table 3.4, the modified versions of the standard models (MRH1, MRH2, MRSH, MRN, MRT), generated less errors for all three time periods considered. The reduction in sum of the squared residuals was significant at the 0.01 level, as observed in Table 3.4.

Further minimization of residuals was acheived by adding derivative components to the standard models. To every steady-state component in a model, a time derivative component was added. As previously, a non-linear regression was used to obtain the best coefficients for each subject during the three time periods (S, C and R). The results of this analysis, shown in Table 3.5, indicate that further reduction in errors occur, when comparing models with derivative terms and personalized coefficients (MRH1DT, MRH2DT, MRSHDT, MRNDT) with models containing the same independent variables as the standard models, but with personalized coefficients (MRH1, MRH2, MRSH, MRN, MRT). Using the F-test described previously, the addition of time derivative terms of the independent variables significantly decreased the error of prediction, at the 0.01 level, when compared to the modified models with no time derivatives (Table 3.4).

Taking into account all the standard models, the modified and transformed versions, a total of fifteen functional relationships between dependent and independent variables were tested. The equations were ranked according to their power of

Table 3.4 : Evaluation of modified versions of standard
    formulae, containing personalized coefficients. The
    calculated F-ratio, when compared to the tabulated value,
    indicates significant reductions ($p < 0.01$) in residuals from
    standard models.

Model	$SSR_0 - SSR_1$[*]	F	F_{TAB}	
			.05	.01
MRH1	1421.87	570.85	3	4.61
MRH2	1172.76	551.11	3	4.61
MRSH	20098.85	9444.95	3	4.61
MRN	4005.27	1566.64	2.6	3.68
MRT	2003.66	714.55	2.6	3.68

[*] Difference between the sum of the squared residuals
generated by the unmodified standard formula, SSR_0,
and the standard formula containing personalized
coefficients, SSR_1.

Table 3.5 : Evaluation of modified versions of standard models incorporating time derivative terms of the independent variables and personalized coefficients. The calculated F-ratio, when compared to the tabulated value, indicates significant reductions ($p < 0.01$) in residuals from the modified models containing personalized coefficients, but no derivative terms.

Model	$SSR_1 - SSR_2$ *	F	F_{TAB}	
			$\alpha = .05$	$\alpha = .01$
MRH1DT	132.19	198.78	3	4.61
MRH2DT	63.24	79.55	3	4.61
MRSHDT	105.37	174.74	3	4.61
MRNDT	18.72	23.7	2.6	3.32

*Difference between the sum of the squared residuals
generated by the standard formula containing
personalized coefficients, SSR_1, and the standard
formula incorporating personalized coefficients and
time derivatives of the independent variables, SSR_2

prediction as indicated by the generated sum of the squared residuals, shown in Table 3.6. Results of this analysis indicate that the best fit to the observed data was obtained using model MRSHDT, as suggested by Stolwijk and Hardy (1966). Next best predictors are models MRH1DT and MRNDT. For pooled cooling data only, model B generates the least amount of residuals. Following model B, the transformed versions of the equations suggested by Hayward et al. (1977), MRH2DT and MRH1DT, are the best predictors . During rewarming , the best predictors are models MRT, MRSHDT and MRH2, respectively.

Of the original standard models, it seems that the formulae suggested by Hayward et al. (1977) offer the best predictive power, over the three time periods considered (Table 3.6). Although the errors generated by H1 are similar in magnitude to the errors generated by H2, model H2 does generate slightly less error. The exception to the above occurs when considering the pooled cooling data of the ten subjects. Under these conditions, model T (Timbal et al., 1976 a,b) proved to be the best predictor, followed by model H2 and H1 respectively (Table 3.6).

Table 3.6 : Residuals generated by various models for pooled
data of ten subjects during cooling and rewarming, S;
cooling only, C; and rewarming only, R.

Model	S	C	R
H1	1699.59	769.9	929.69
H2	1409.59	623.95	789.05
SH	20336.2	12938.27	7397.93
N	4194.46	3285.43	909.54
T	2211.16	580.71	1630.15
MRH1	277.72	70.25	50.93
MRH2	237.24	52.07	43.75
MRSH	237.35	50.97	77.19
MRN	189.19	52.1	52.0
MRT	207.5	60.35	29.37
MRH1DT	145.53	49.28	46.89
MRH2DT	174.0	36.68	73.05
MRSHDT	131.98	71.03	30.25
MRNDT	170.47	51.34	69.03
B	631.03	6.83	68.74

S - cooling and rewarming data (pooled data of all subjects)
C - cooling data only (pooled data of all subjects)
R - rewarming data (pooled data of all subjects)

V. Discussion

Of the standard formulae investigated, the equations suggested by Hayward et al. (1977) offer best predictions when cooling and rewarming periods are treated together. Model H2, utilizing tympanic temperature as an indicator of core temperature, offers some advantage when compared to H1, which differs only in the fact that it uses rectal temperature as indication of the thermal state of the core.

It is not surprising that model N is a better predictor than SH, as Nadel et al. (1970), based their model on SH and suggested that their modification accounted for the increased metabolic rate due to a decrease in peripheral temperature, with no alteration in core temperature; a situation usually present during the first several minutes of immersion in cold water. Although the model of Nadel et al. (1970) loses two degrees of freedom when statistically evaluating its predictive power, due to the fact that it has two additional parameters, this also offers some advantage when attempting to derive predictive expressions.

The model of Timbal et al. (1976 a,b), although quite advanced in its attempt to model the metabolic response in air and water, did not offer better predictions than the model of Hayward et al. (1977), for the given subject pool. It did, however, generate less errors than model N, when cooling and rewarming data was treated together.

With due consideration to the authors of the original models, the regression analyses they conducted to obtain the form of the standard equations were performed using data obtained during cooling of human subjects only. It is not surprising to find that they lack in predictive power, when trying to fit their models to data obtained during cooling and rewarming together. With the exception of models SH and and N, the standard models investigated (H1, H2 and T) were observed to give better predictions during the cooling period, as can be seen from Table 3.6. The same table reveals that the best functional relationship for cooling data alone was obtained with the postulated model of Brown and Brengelmann (1970). Obtaining the coefficients for their model from a best fit analyses using the data of Morrison et al. (1982), their model generated the least amount of residuals. The Brown and Brengelmann model is unique in the sense that it considers the thermal controlling mechanism as a closed loop system with negative feedback. Their predicted value of shivering thermogenesis is corrected for rates of change of metabolic rate. Although they allow for changes in metabolic rate and peripheral temperature, they disregard the contributions from core temperature.

The present analysis indicates that the most often used predictive formulae for modelling the metabolic response to cooling offer a varying degree of accuracy. With the results obtained, it is not possible to gain insight into the causes of the errors generated by the models. For a clearer understanding

of the errors, an analysis of the residuals was conducted. If the model is accurate, then ei are the observed errors, which have the following characteristics :

1. they are independent.

2. $\sum_{1}^{N} (ei/N) = 0$

3. σ^2 = variance = constant.

4. ei are normally distributed

The above assumptions are necessary when conducting regression analyses and F-tests (only the last assumption is mandatory for the F-test). An analysis of residuals should indicate whether the assumptions have been violated or not. Although such an analysis may be numerical or graphical in nature, Draper and Smith (1966) suggest that in general regression situations a numerical analysis of the effect of correlation between residuals is not essential, if a graphical analysis is utilized.

If the residuals are evenly distributed about the abscissa, when plotted as a time sequence (Fig. 3.1.a), the indication is, that there exists no time dependent factor which is contributing to the errors. In the case of a time dependent factor being omitted from the model, the graphical plot may be one of the
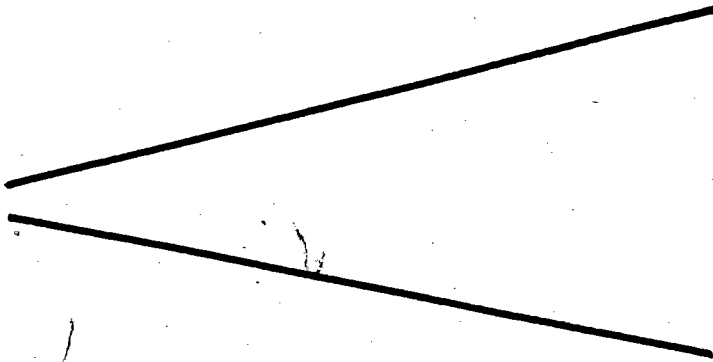
Fig. 3.1 : General responses of residuals, when plotted as a
time sequence. Adapted from Draper and Smith (1970).
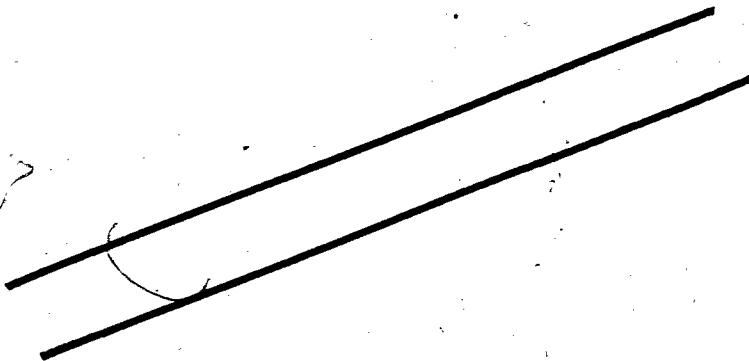
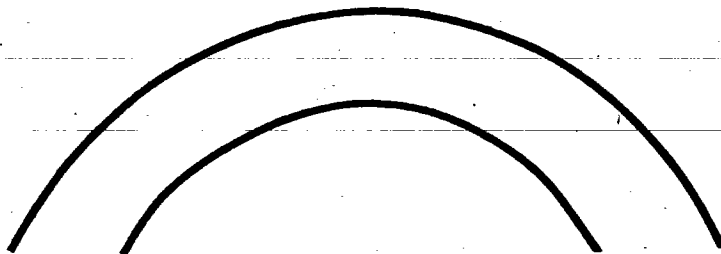# Time sequence plots of residuals

a)

b)

c)

d)

possibilities shown in Fig. 3.1.b,c,d (Draper and Smith, 1966).
It is evident, that a simple analysis of :

$$\sum_{1}^{N} e_i = 0$$

would not have identified such discrepancies.

A plot of the normalized percent residuals against time for one subject (indicative of the response of the majority of the subjects) is shown in Fig. 3.2. The residuals were generated by the standard model ,H2, which gave the best predictions of all the standard models. Fig. 3.2 reveals that a linear or quadratic term in time may have to be included in the model, if it is to model the metabolic response during cooling and rewarming. The response seen in Fig. 3.2 is similar to one of the possibilities suggested by Draper and Smith (1970) and shown in Fig. 3.1.d. By observing the error distribution over a long period of time and obtaining appropriate terms to minimize the error, short term time depenedent factors may be neglected. An example of this is given in Fig. 3.3. For this particular subject (whose residual distribution was unique among all the subjects), the time dependent factor seems to be of a short term nature in contrast to the long term time effect observed in Fig. 3.2. A residual analysis of the models proposed by Stolwijk and Hardy (1966) and Nadel et al. (1970) reveal a relationship shown in Fig. 3.1.c, only with a downward trend, suggesting the inclusion of a linear function in time in the model.

Fig. 3.2 : Time sequence plot of residuals geberated by model H2; long term time dependent factor affecting prediction.
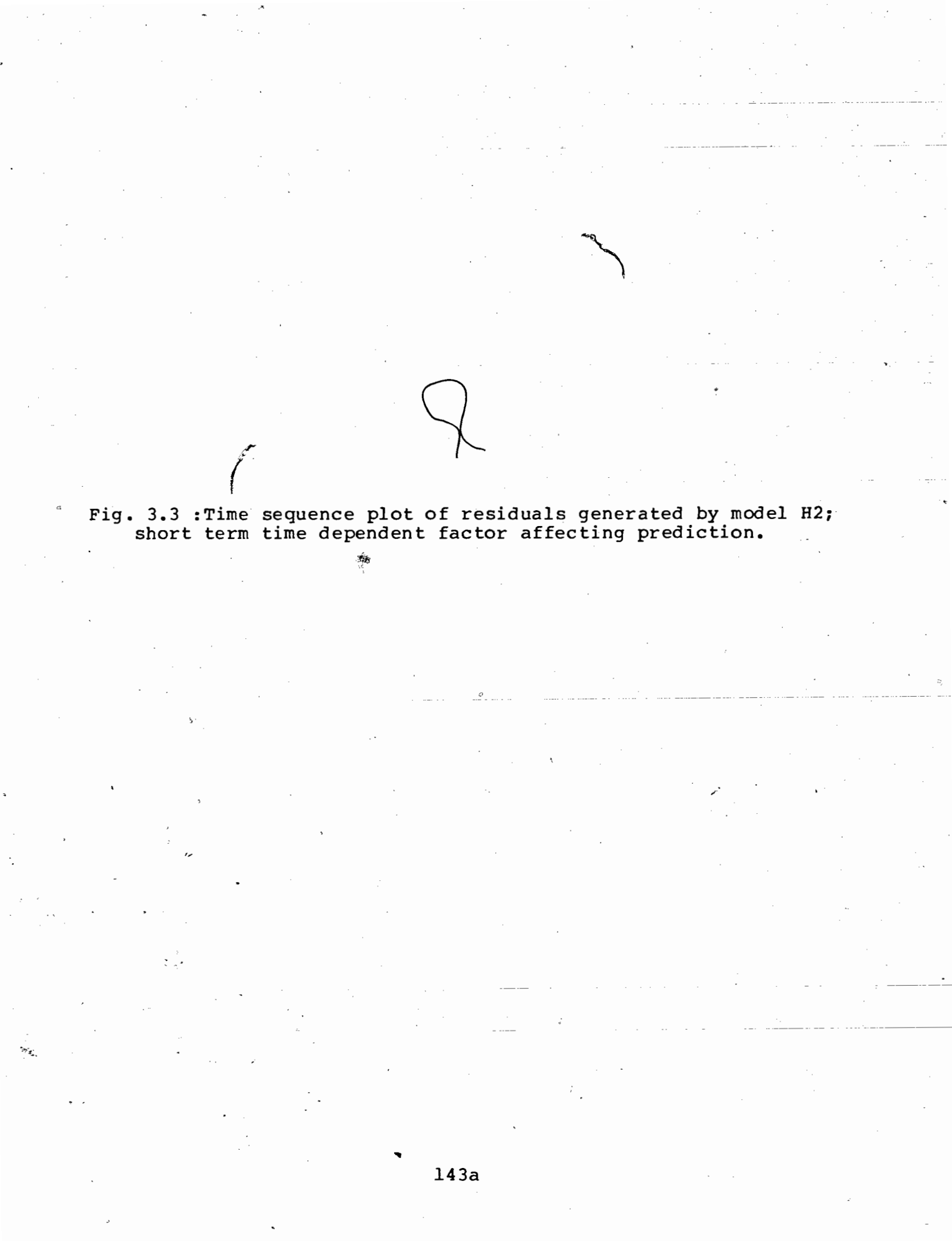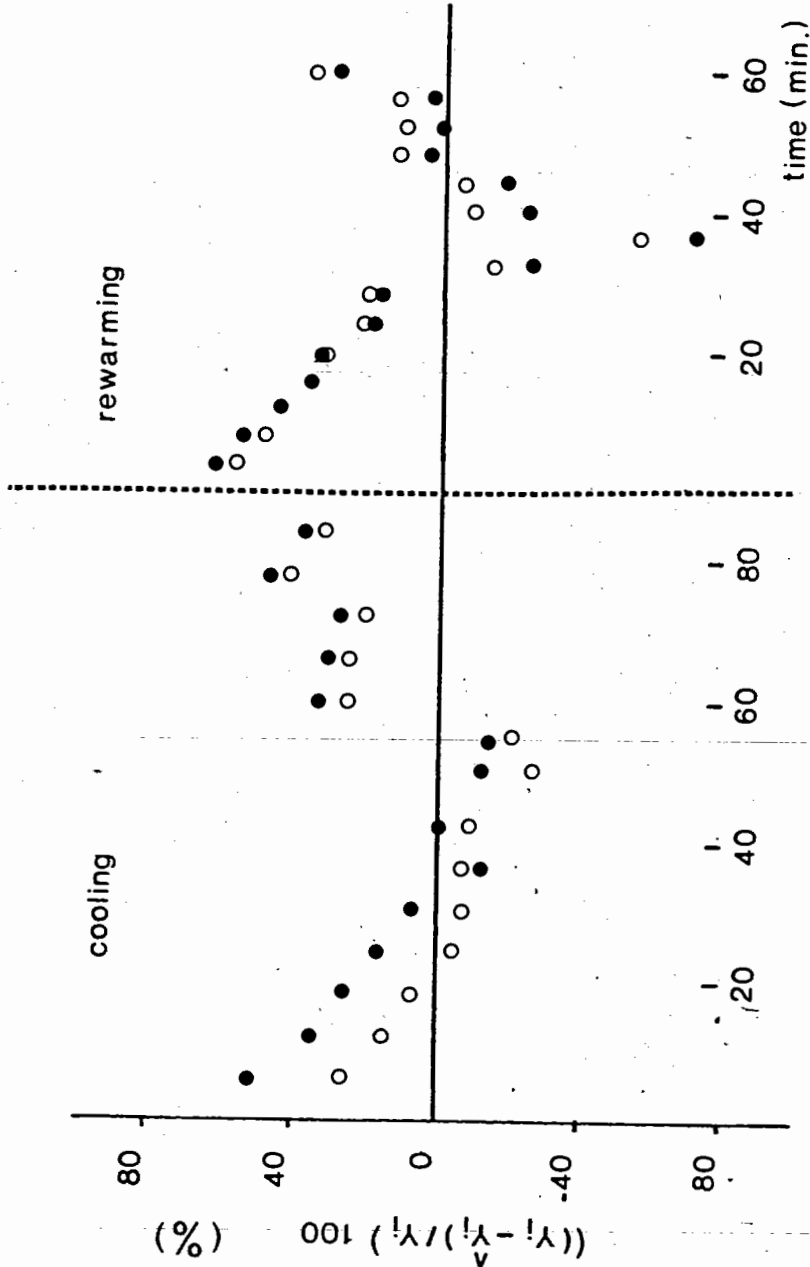
142b
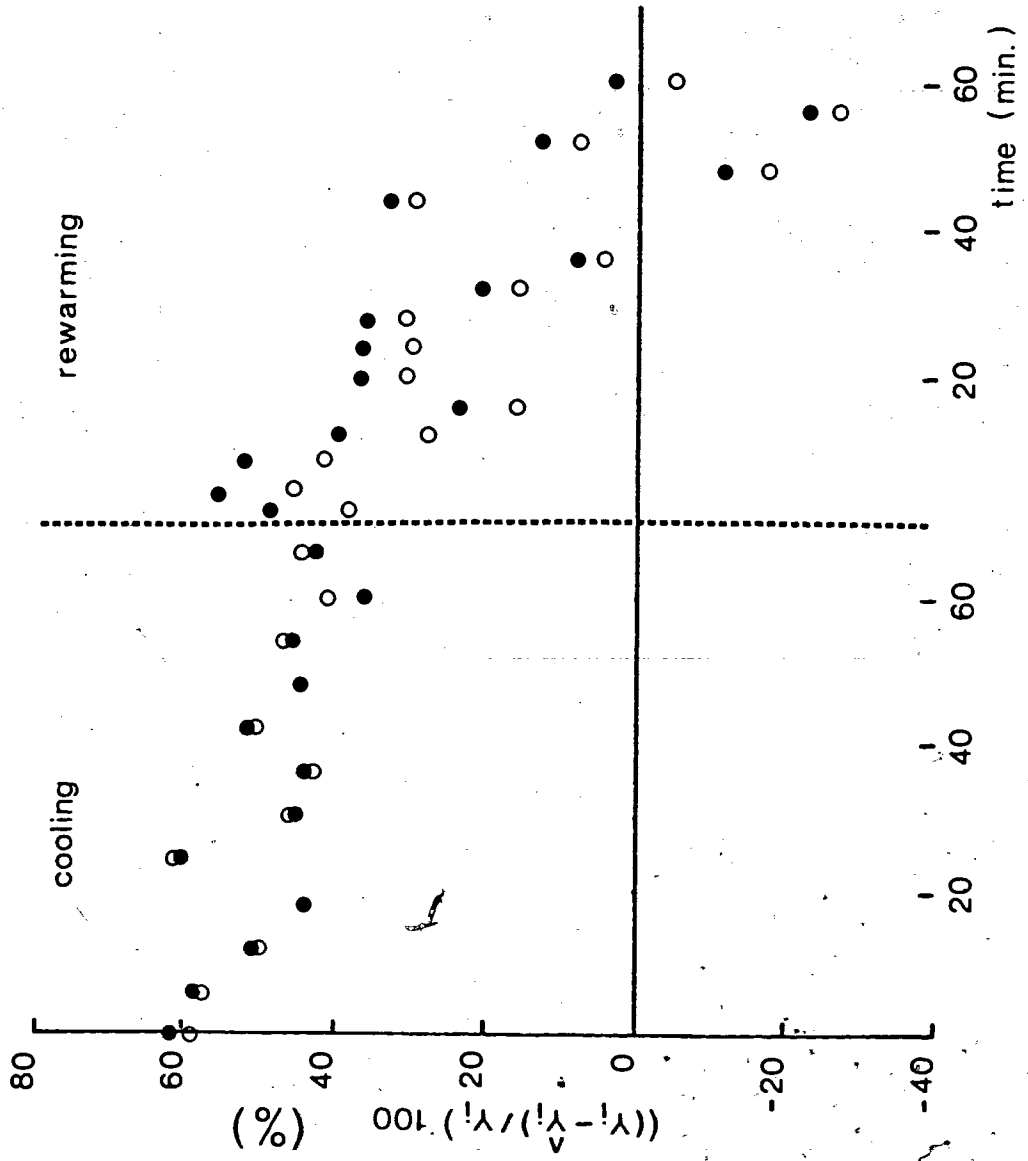
Fig. 3.3 :Time sequence plot of residuals generated by model H2;
short term time dependent factor affecting prediction.

Having established the existence of a substantial time dependent factor, which has been omitted in the majority of the models tested, it is necessary to determine how this factor can be accounted for in the models. From the empirical relationships proposed by models H1, H2, SH and N, it is evident that the predicted value, $\hat{Y}0$, is a linear function of peripheral and core temperature:

$$\hat{Y}0 \propto f \; (Tperiphery, \; Tcore) \qquad \qquad ...(3.28)$$

and that these independent variables are time dependent.

The time sequence plots of the residuals (Fig. 3.2 and 3.3) suggest that a time dependent term should be added to the model. This could also be interpreted as an inadequate functional relationship between the metabolic rate and the independent variables, namely skin and core temperature. This is illustrated with the plot of the normalized percent residuals (for models H1 and H2) against the independent variables, skin temperature (Fig. 3.4) and core temperature (Fig. 3.5). If the residuals are distributed about the abscissa (independent variable), as previously shown in Fig. 3.1.b,c,d then the relationship between the dependent and independent variable is lacking. The bell shaped curve in Fig. 3.4, indicates that skin temperature should be weighted with a quadratic term in the model or that a transformation of the dependent variable is necessary. There is

Fig. 3.4 : Plot of percent error generated by models H1 and H2
    as a function of peripheral temperature.

T_s (°C)

34

30

26

22

18

$$(\hat{\gamma}_i - \gamma_i)/(\gamma_i)\ 100\ (\%)$$

80

40

0

−40

−80

H1: ■ cooling
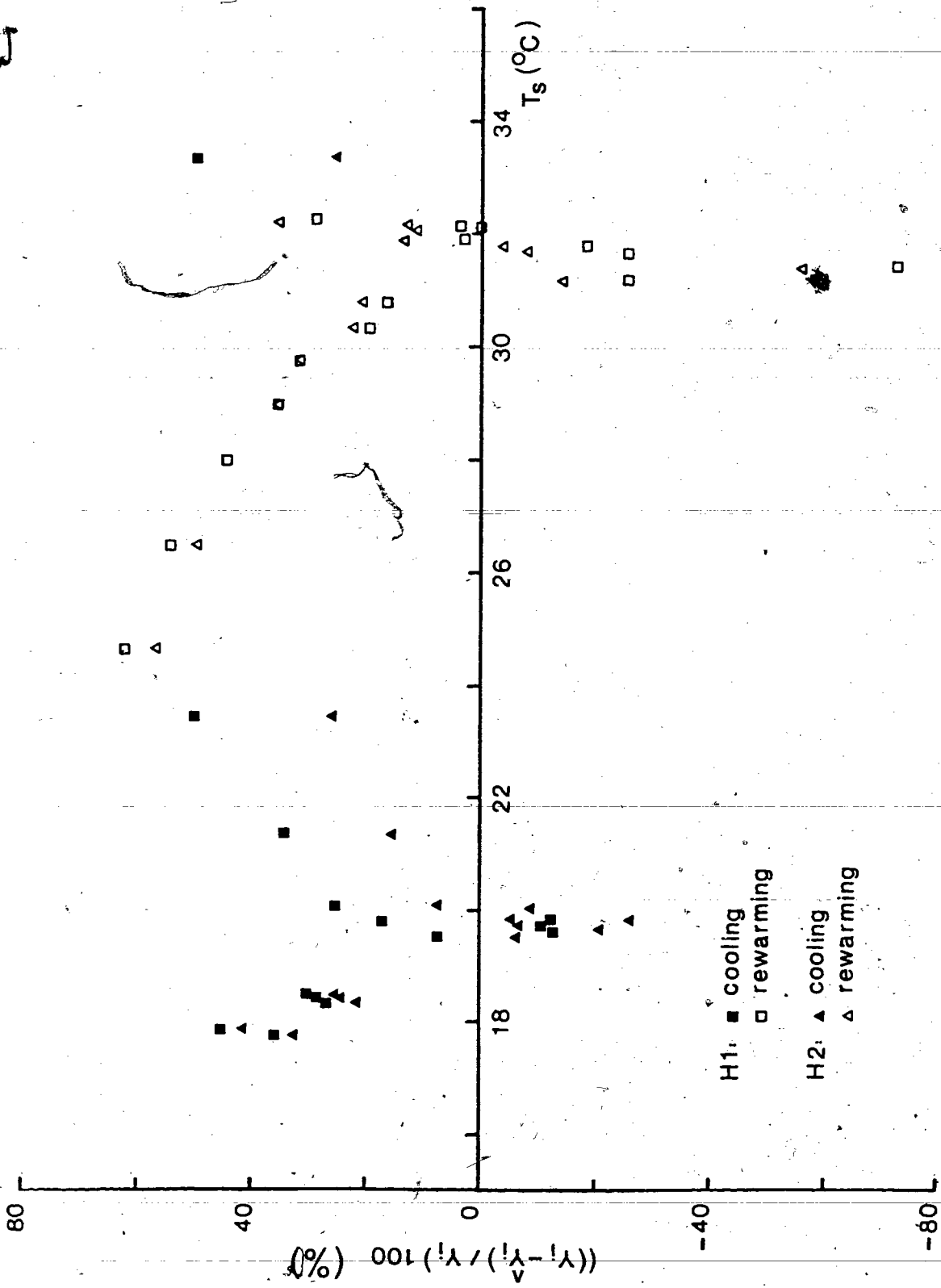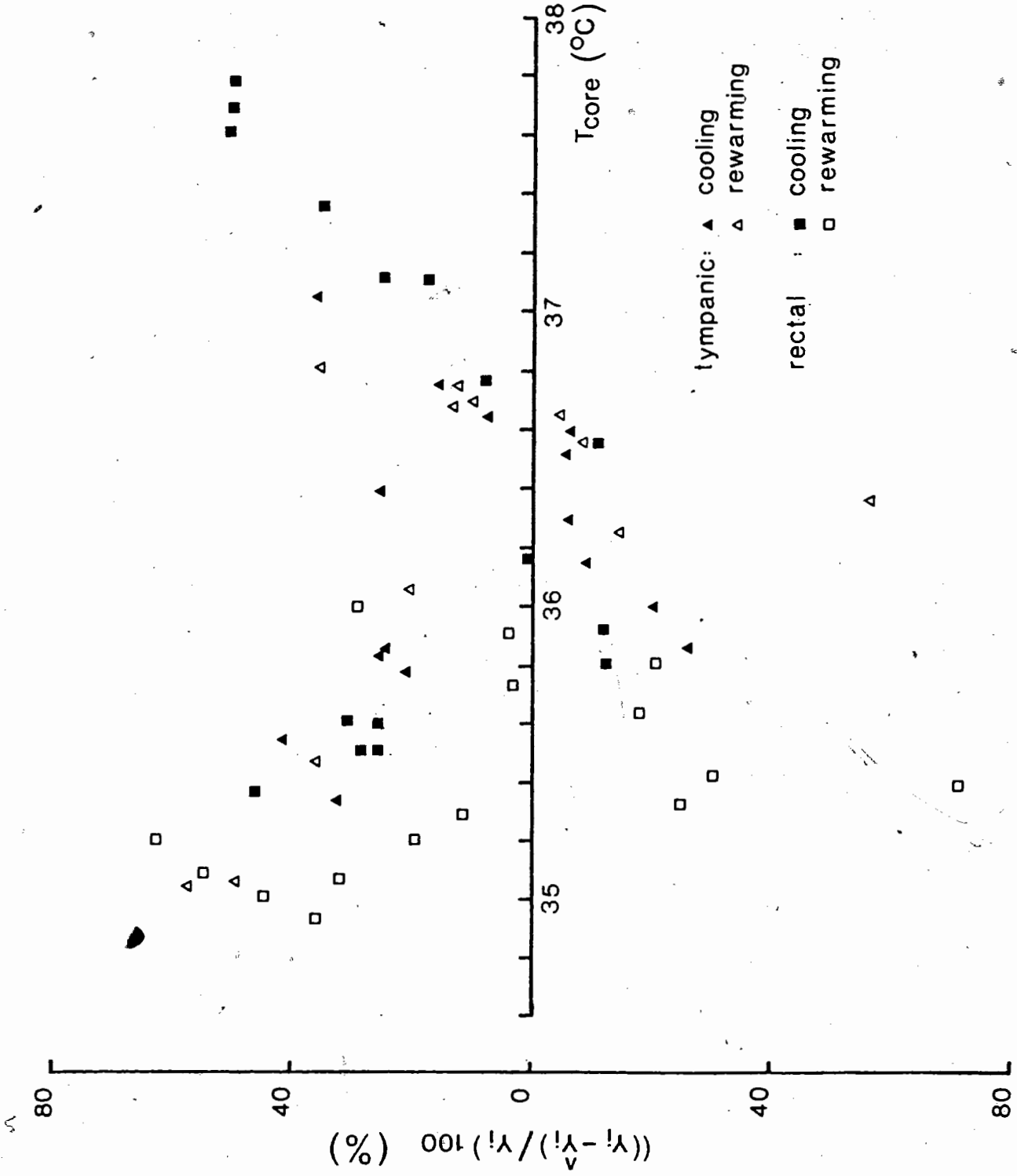□ rewarming

H2: ▲ cooling
△ rewarming

145b

Fig. 3.5. : Plot of percent error generated by models H1 and H2 as a function of core temperature.

146b

experimental evidence to suggest that the origin of this relationship of the residuals against skin temperature stems from the sensitivity of the temperature transducers in the skin (the cold receptors) and their influence on metabolic rate. The sensitivity of cold receptors to steady state thermal stimuli has been reported by Zotterman (1953) and is presented in Fig. 3.6. The average firing rate of cold receptors varies with temperature and reaches a maximum at approximately 25°C. A second peak in discharge rate was observed at temperatures of approximately 10°C; below this temperature the sensitivity of the cold receptors is negligible and the pain receptors, some of which are also thermosensitive, begin to fire (Guyton, 1976). Hensel (1976) has proposed that the steady state characteristics of cold receptors, at the temperatures at which these receptors are most sensitive, are similar to the metabolic response observed in humans at similar temperatures of the skin (Fig. 3.7).

Comparing Fig. 3.4 and Fig. 3.6, it can be seen that the plot of the residuals over a range of skin temperatures is very similar to the average sensitivity of the cold receptors for the same range of skin temperature, which in turn has a similar response as metabolic rate (Fig. 3.7). This would suggest, that skin temperature should be weighted according to the sensitivity of the cold receptors at any given skin temperature.

Since the existence of cold receptors in the viscera has been confirmed (Rawson and Quick, 1971, 1972), a similarity in

Fig. 3.6 :Steady state discharge characteristics of peripheral
    cold (closed circles) and warm (open circles) receptors.
    Adapted from Zotterman (1970).
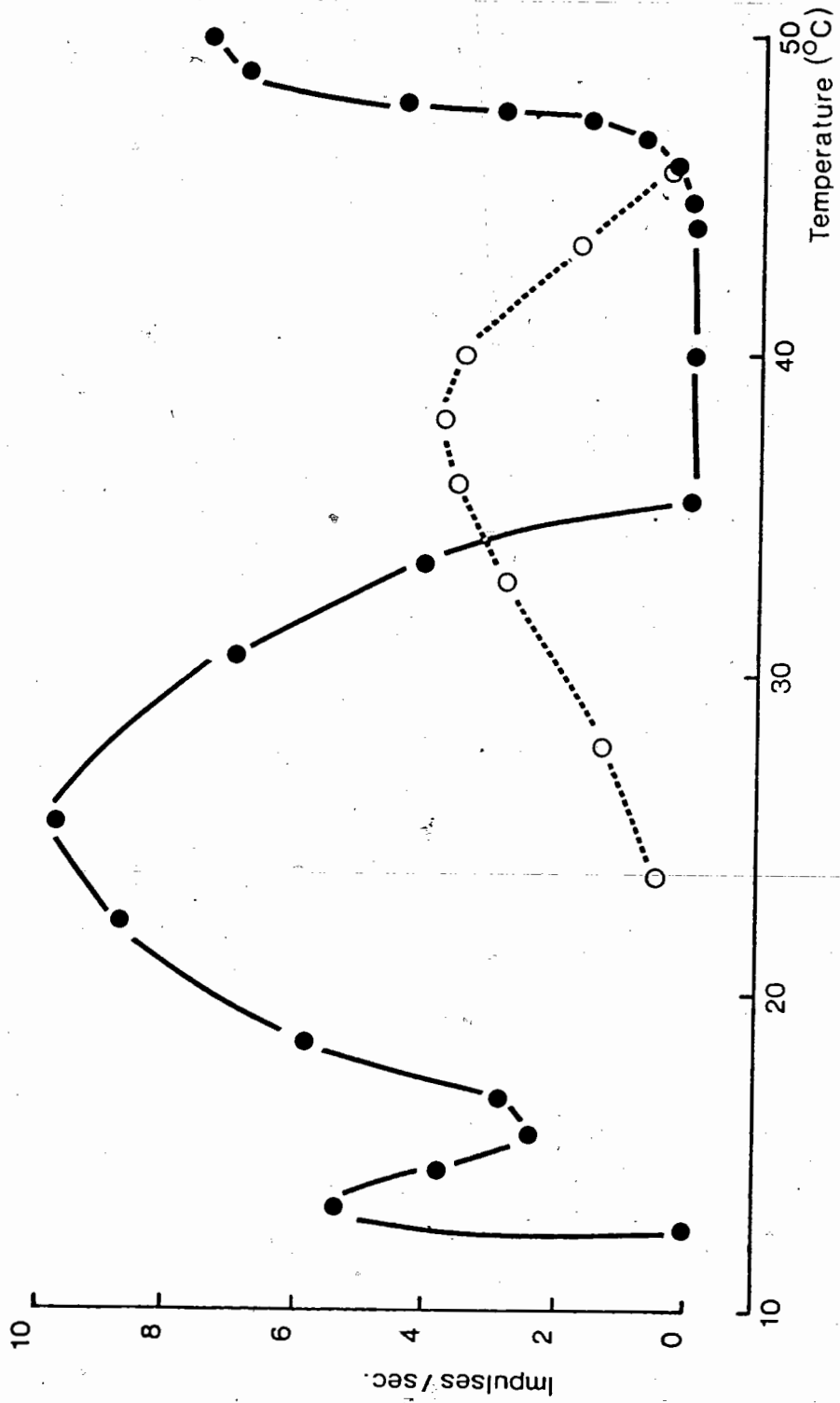
148b

Fig. 3.7. : Comparison of average static frequency of cold
    fibers in monkeys (closed circles; Dykes, 1975) and
    metabolic rate in man (open circles; Benzinger, 1969), as a
    function of skin temperature. Adapted from Hensel (1976).

Skin temperature ($^{\circ}$C)

Relative units

149b
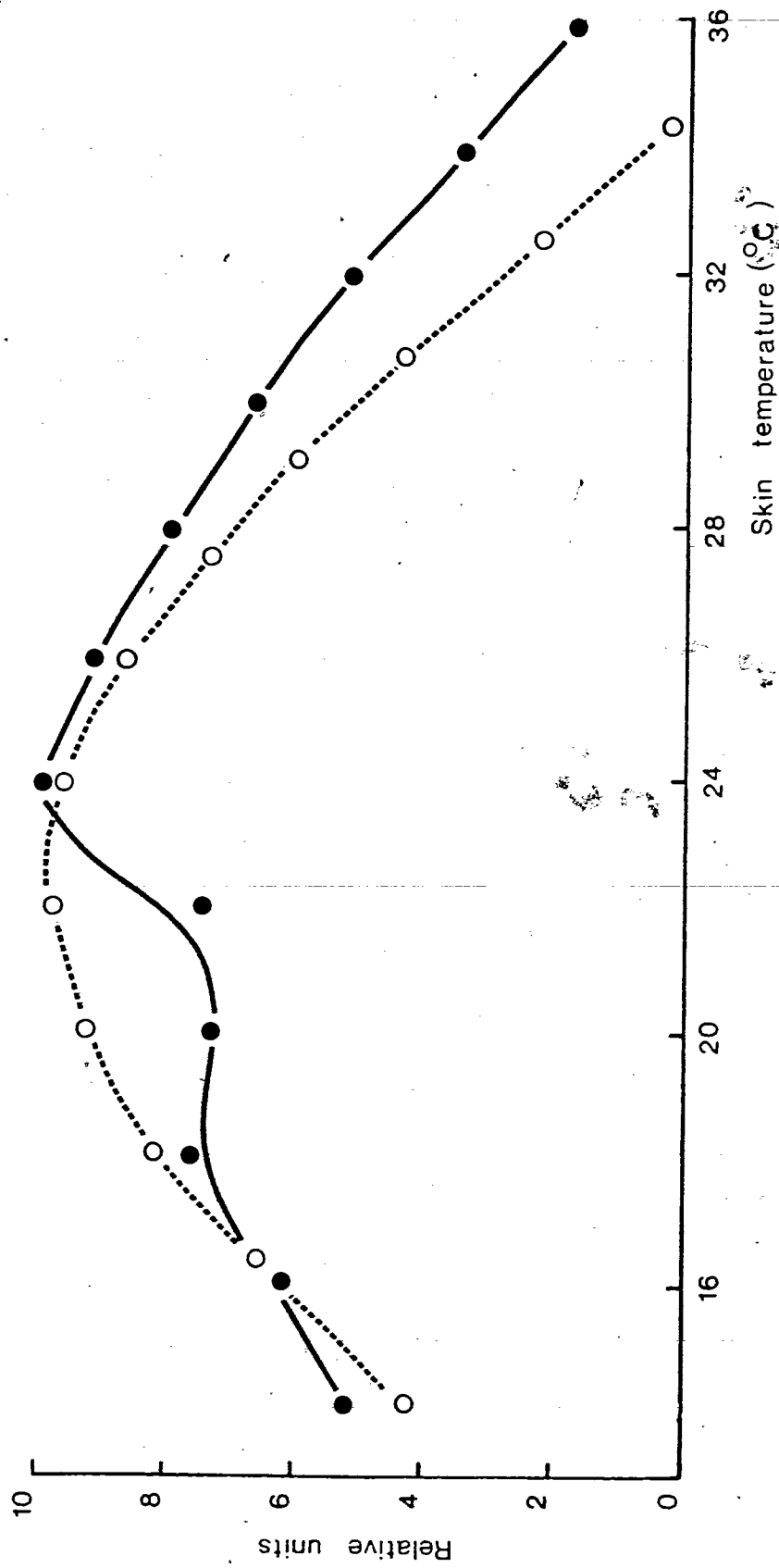
the metabolic response and cold receptor sensitivity may be expected, assuming that the core cold receptors have a similar average steady state discharge response as the skin cold receptors. This relationship cannot be observed over a wide range of core temperatures, as core temperatures are normally not allowed to fall below $35^{\circ}C$ in human experimentation, excluding the 'after drop'. From the data obtained by Benzinger (1970), it seems that this hypothesis may be true. As core temperature drops, at a constant skin temperature implying increasing sensitivity of only the core cold cold receptors, metabolic rate increases proportionately. In other words, a similar relationship between core cold receptor sensitivity and metabolic rate may exist as depicted in Fig. 3.7 for the skin cold receptors and metabolic rate. Although the shape of the curves may be similar, they would have to be shifted towards higher temperatures for the core. According to the set-point theory (Benzinger, 1969), metabolic rate begins to increase once core temperature falls below $37.1^{\circ}C$. Analysing the plot of the normalized percent residuals at various temperatures of the core in Fig. 3.5, it appears that the residuals are at a minimum at a core temperature of $36.6^{\circ}C$. Above this temperature, the residuals increase proportionately.

It would therefore appear, that an appropriate modification to the models would be to weight the steady state core and skin temperatures according to the average sensitivity displayed by the cold receptors. Although the relative response of metabolic

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rate may be similar, the gain of the (core receptor responsiveness)/(metabolic rate) control loop may be greater. The physiological range over which core cold receptors contribute to the metabolic rate is approximately 37° to 32°C. Above core temperatures of 37°C the heat loss mechanisms are initiated by central warm receptors (Benzinger,1970). Below core temperatures of 32°C shivering thermogenesis is abolished (Maclean and Emslie-Smith,1977), thus decreasing the metabolic rate.

Modifying the models by weighting core and skin temperature according to the sensitivity of the cold receptors may not be adequate in improving the predictive power of the relationships. The response of cold receptors does not depend on the temperature of cold receptors alone, but also on the temperature gradient. Thus the contribution of the rate of change of temperatures (core and skin) to the metabolic rate, if such a relationship exists, will be a function of both the temperature gradient and the cold receptor sensitivity at any instantaneous adaptive temperature.

As yet, the contributions of dynamic core and peripheral temperatures to the metabolic response have not been experimentally quantified. Therefore, it is not possible to suggest the errors that would be generated by the omission of these terms in a predictive model. An indication of the errors due to the omission of these time derivatives in the models, is possible by simultaneously plotting the normalized percent error

of prediction and dTs/dt, dTr/dt and dMR/dt against time, as shown in Fig. 3.8. The graph illustrates that the greatest errors in prediction (expressed as normalized percent error) observed, coincide with regions, where the dynamic components of skin and core temperature are the greatest. The dynamic overshoot in metabolic rate observed at the onset of cold exposure (Benzinger, 1969; Hayward et al., 1977) has been explained as a response to the rapid change of skin temperature alone (Benzinger, 1969). Although Hayward et al. (1977) aknowledge this overshoot, their model is not capable of predicting metabolic rate in this region of cooling. The omission of dTs/dt would therefore result in errors at the onset of cooling. The rapid cooling of the skin is seen as a negative peak in skin cooling rate (dTs/dt) in Fig. 3.8. The resultant increase in metabolic rate is also evident from Fig. 3.8. The metabolic overshoot is not as evident from this data, as metabolic rate was sampled every six minutes and the overshoot may occur within the first several minutes of the cold water immersion. Nevertheless, the rapid change of dMR/dt as a result of increasing dTs/dt is reflected as a 40% increase in the normalized error. Once the temperature of the skin has stabilized at a level slightly higher than the temperature of the water, as evidenced by the zero rate of change

Similar inaccuracies are apparent at the onset of rewarming, where the skin temperature rises rapidly, while the core temperature continues to drop. There is an increase in the
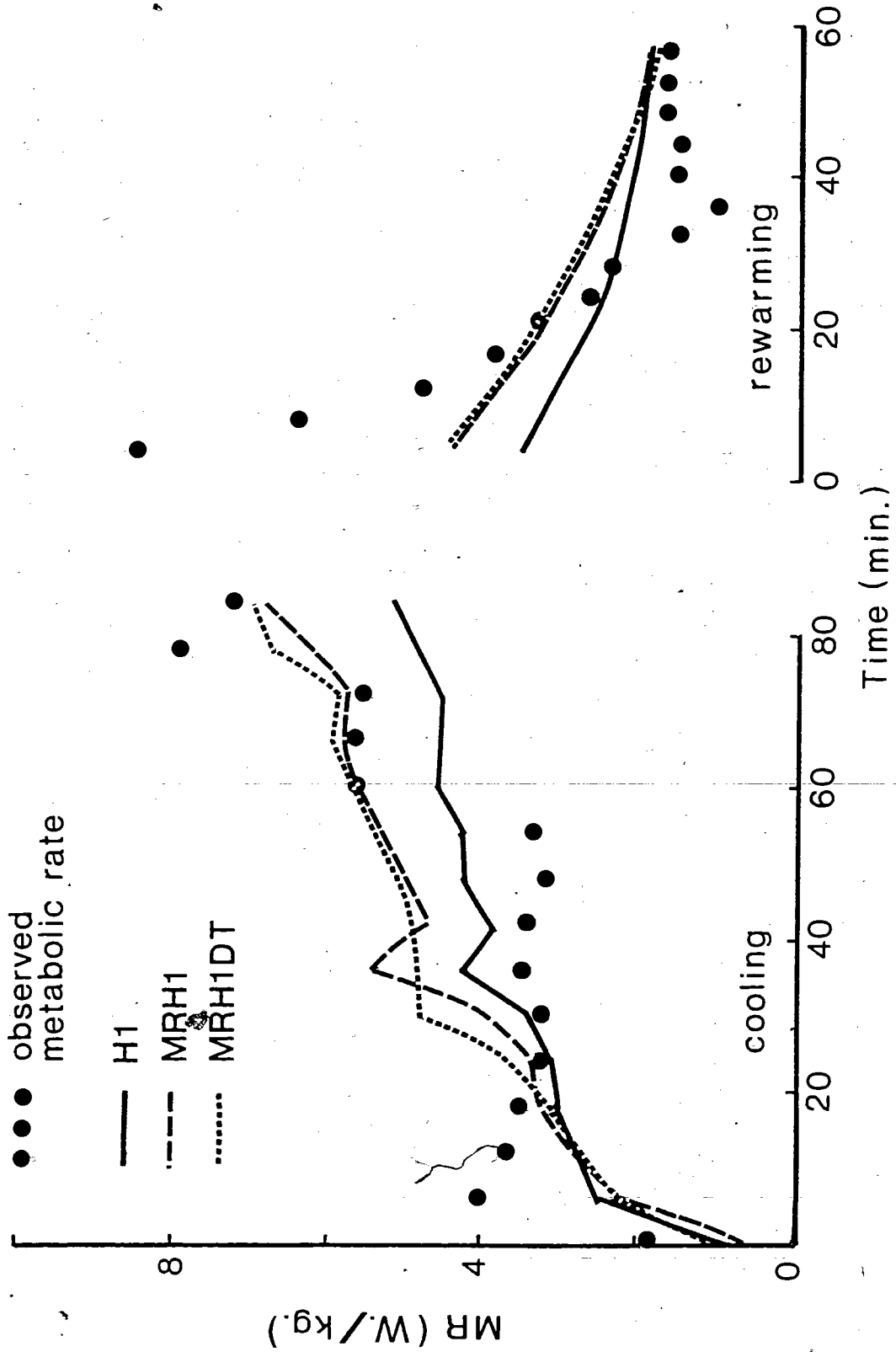
Fig. 3.8 : Comparison of the responses of percent error and the
     dynamic responses of core and peripheral temperature and
     metabolic rate during cooling and rewarming.

COOLING   REWARMING

153b
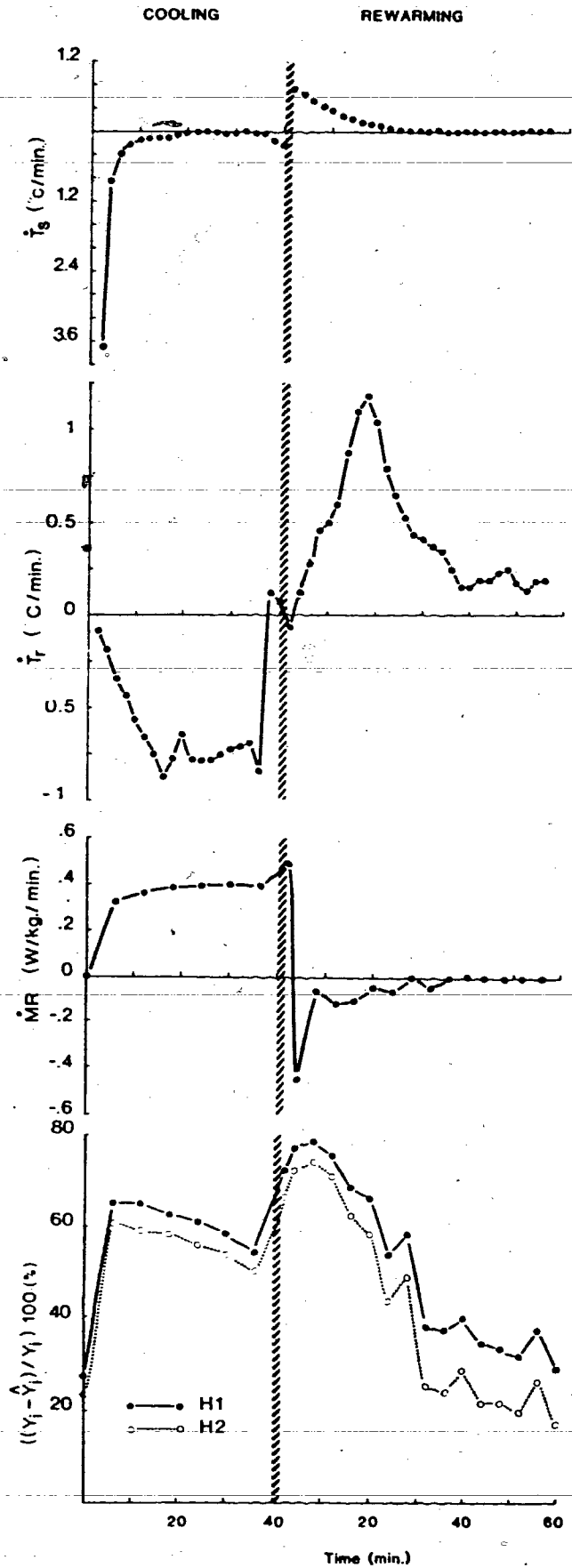
normalized error at the onset of rewarming, concomitant with the increase in the rate of rise in skin temperature. As the rate of change of dTs/dt approaches zero, the normalized percent error also decreases. However, the normalized percent error decreases in two stages. In the first 30 mintues of rewarming the normalized percent error decreases slower than in the final 30 minutes of rewarming. This difference may be explained by the response of the time derivative of rectal temperature, dTr/dt, during this time period. In the first half of the rewarming period, core temperature accelerates to a peak value of rewarming rate (Fig. 3.8), followed by a decrease in the rewarming rate to a fairly constant level. The errors eventually become negligible as core temperature reaches normothermic values, coinciding with smaller changes in core temperature over a given time period.

In conclusion, the present study emphasizes the inadequacies of existing models predicting thermogenesis in humans. As seen in Fig 3.9, the prediction of existing models has been enhanced by statistical manipulation rather than by consideration of physiological responses. It is hypothesized that the predictive power can be dramatically improved, by including weighting factors for skin and core temperatures. Residual analysis indicates that these factors should incorporate neural response characteristics of thermoreceptors in peripheral and core regions. The present study also suggests, that omission of time in thermoregulatory models may decrease

Fig. 3.9 : Comparison of predictions of model Hl, MRHl and
    MRHlDT .

Figure legend:
- observed metabolic rate (●●●)
- H1 (——)
- MRH1 (– – –)
- MRH1DT (·······)

Axes: MR (W./kg.) vs Time (min.)

cooling / rewarming

155b

the predictive power of such models. Models neglecting time will generate substantial errors with increasing magnitudes of skin and core temperature transients.

VI. References

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D. CONTRIBUTION OF PERIPHERAL AND CORE STATIC AND DYNAMIC

TEMPERATURES TO THE THERMOGENIC RESPONSE IN MAN

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I. Introduction

The milestone discoveries of 'thermogenic' and 'thermolytic' centres in the preoptic hypothalamus by Isenschmid and Krehl (1912) and Aronsohn and Sachs (1885) respectively, represented the beginnings of modern thermoregulatory physiology. A great deal of emphasis has been placed since these discoveries, on quantifying the response of the thermoregulatory centres to given thermal stimuli (for reviews see Hammel, 1968; Bligh, 1973; Hensel, 1982).

The thermogenic or heat production, centre in the pre-optic posterior hypothalamus receives information from peripheral temperature sensors (Zotterman, 1953; Vallbo et al., 1979) as well as from structures within the body core (Rawson and Quick, 1971, 1972). During extremes of cold, thermal information is integrated at the spinal level (Lim, 1960; Simon, 1972, 1974) and then conveyed via ascending fibres in the spinal cord (Simon and Iriki, 1970, 1971a,b), reticular formation in the brainstem (Nakayama and Hardy, 1969) and mid brain raphe nuclei (Dickenson, 1976) to the thermogenic centre within the posterior hypothalamus. This centre activates thermoregulatory processes, such as an increase of metabolic rate, followed by shivering and the heat conserving mechanisms of vasoconstriction and piloerection (Folkow, 1955).

Although Aronsohn and Sachs (1885) are credited for the discovery of the heat loss centre, by demonstrating increases in

rectal temperature in cats as a result of electrical stimulation of this centre, the thermosensitivity of the heat loss centre was established by Barbour (1912). Barbour observed that thermal stimuli applied with water perfused thermodes induced vasoconstriction and vasodilation, when cold and warm water was used respectively. It has been shown by Hemingway et al. (1940) that this centre exerts an inhibitory influence on the preoptic posterior hypothalamus. Therefore, the metabolic response to a cold stimulus would be a result of a combination of thermal signals originating at the periphery, body core (visceral and intra-abdominal region) and the central nervous system.

It has been suggested that the human thermoregulatory control system is analogous to a thermostat (Barbour ,1912), which maintains internal body temperature with an 'adjustable set-point' (Hammel et al., 1963). Empirical evidence for a physiological 'set-point' has been reported by Benzinger (1969), who proposed the theory of central inhibition of thermogenesis. Implications of this theory are that, regardless of skin temperature, metabolic rate will remain unaltered unless central temperature decreases below a certain set point (according to Benzinger's results this is at a tympanic temperature, T_{ty}, of 37.1° C). Below this point the metabolic rate will rise parabolically, the rate of increase being dependent upon the level of skin temperature.

Benzinger's concept of the metabolic response to a cold environment has been widely accepted, although there is still

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disagreement as to the numerical relationship between metabolic rate and steady state skin and core temperature (Craig and Dvorak, 1966). Brengelmann (1967) has challenged the results of Benzinger, suggesting that tympanic temperatures as reported by Benzinger were decreasing and could therefore not be termed static but rather should be considered as being 'quasi-steady state'.

Contrary to the suggestions of Stolwijk and Hardy (1966) that,

> 'any output (from sensors) corresponding to the rate of change of local temperature is ineffective in the (thermo-)regulating process',

it has been suggested that the metabolic overshoot evidenced in the initial stages of cold water immersion is a result of peripheral cold stimulation (Benzinger, 1969); Hayward et al., 1977). In hot environments, there is also evidence that the rate of change of skin temperature has a significant influence on the sweating mechanism, a part of the thermoregulatory control system (Wurster and McCook, 1969; Libert et al., 1978, 1979).

Despite extensive studies on the static and dynamic characteristics of peripheral cold and warm receptors by Zotterman (1953), Hensel and Boman (1960), Kenshalo and Duclaux (1977) and Duclaux and Kenshalo (1980), only suggestions have been made implicating peripheral temperature transients in the magnitude of the metabolic response (Hong and Nadel, 1979). Piantadosi et al. (1981) have studied the metabolic response to core cooling in a hyperbaric environment and suggested that

increased cooling rates may be accompanied by greater metabolic rates.

Hensel (1976) has shown that the static firing characteristic of a cold fibre population of a primate is identical to oxygen consumption of humans for a range of skin temperature (Tskin 14° - 36° C), if they are scaled to relative units. However, there is still inconclusive evidence to support the hypothesis that the dynamic characteristic of cold receptors as a result of temperature transients at the receptor site (either the periphery or core) contribute to the thermogenic response in man.

Studies investigating the controlling mechanisms of the human thermostat can employ numerous experimental procedures. Usually such studies are undertaken in environmental chambers (Cunningham et al., 1978), thus including radiative, conductive, convective and evaporative pathways of heat loss. In order to minimize the number of variables and hence the complexity of the investigation, subjects can be immersed in water, thereby eliminating heat loss by radiation and evaporation from the skin surface. Heat loss by evaporation will still be present from the respiratory tract; in the case of a head-out immersion, there will be considerable heat loss by evaporation and radiation from the head (Wissler, 1970).

In the analysis of the thermoregulatory control system, it is preferable to control the input signal (thermal stimulus) and subsequently monitor the output signal (response of

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thermoregulatory effector mechanism). An experimental procedure capable of maintaining adequate control of the input variables and allowing various functions to be introduced to the control system under observation, is essential. This type of control may be achieved by means of a water perfused suit (Rowell et al., 1969). Such a suit is capable of maintaining a constant temperature stimulus to the skin, or imposing either a step or ramp change in the thermal stimulus.

In order to observe the onset and development of hypothermia during maritime accidents, several studies have been conducted immersing subjects in tidal waters (Hayward et al. 1977). Although such studies are essential for a better understanding of the progress of accidental hypothermia, as a means of analysing thermoregulation they are limited by uncontrollable environmental factors such as ambient temperature, wind velocity, humidity, water currents and most important water temperature. A laboratory study is preferable therefore, if an analysis is to be made of the response of the thermoregulatory control system to various thermal stimuli, as it allows control of the above mentioned variables (Morrison et al. 1982; Brengelmann, 1967; Martin, 1977).

The present study attempts to: 1) confirm the relationship between static core and peripheral temperature and metabolic rate, 2) quantify the metabolic overshoot during the initial stage of cold water immersion with respect to the temperature gradient imposed on the peripheral temperature receptors and 3)

elucidate the role of core temperature transients at various

clamped skin temperatures in the increase of thermogenic drive.

II. Methods

Subjects

Five male volunteers participated in the present immersion study. The subjects' characteristics are presented in Table 4.1. Permission for their participation was also obtained from a physician, following a medical examination. Using the method proposed by Carter (1980), each subject's somatotype was estimated, as shown in Fig. 4.1.

A physical work capacity test (P.W.C. 170) was administered to all the subjects, to predict their level of fitness. The experimental procedure consisted of the subjects riding a programmable, electrically braked bicycle ergometer (Quinton Instrument Co.). A step increase of work rate was applied every five minutes, thus allowing the heart rate to stabilize at each particular workload. During the P.W.C. 170 test, values of oxygen uptake were obtained for each level of exercise. Table 4.1. depicts the oxygen uptake achieved at a workrate demanding a heart rate of 170 beats/minute, for each subject.

Table 4.1 : Subjects' physical characteristics.

Subject	Age	Weight	Height	PWC_{170}/kg.	Percentile	VO_2 at a heart rate of 170 beats/minute.
	yrs.	kgs.	cms.	kg./m./min.	°/oo	ml.O_2/kg./min.
AL	24	84.4	184.6	16.42	75	39.0
BC	22	70.9	180.5	16.97	80	44.0
DS	27	87.3	178.2	16.28	45	39.3
DT	26	73.7	175.5	16.28	75	37.5
RH	26	70.1	188.8	17.22	80	39.0

Fig. 4.1 : Subjects' somatoplots.
    Derived according to the principles outlined by Carter
    (1980).

mesomorphy

endomorphy

ectomorphy
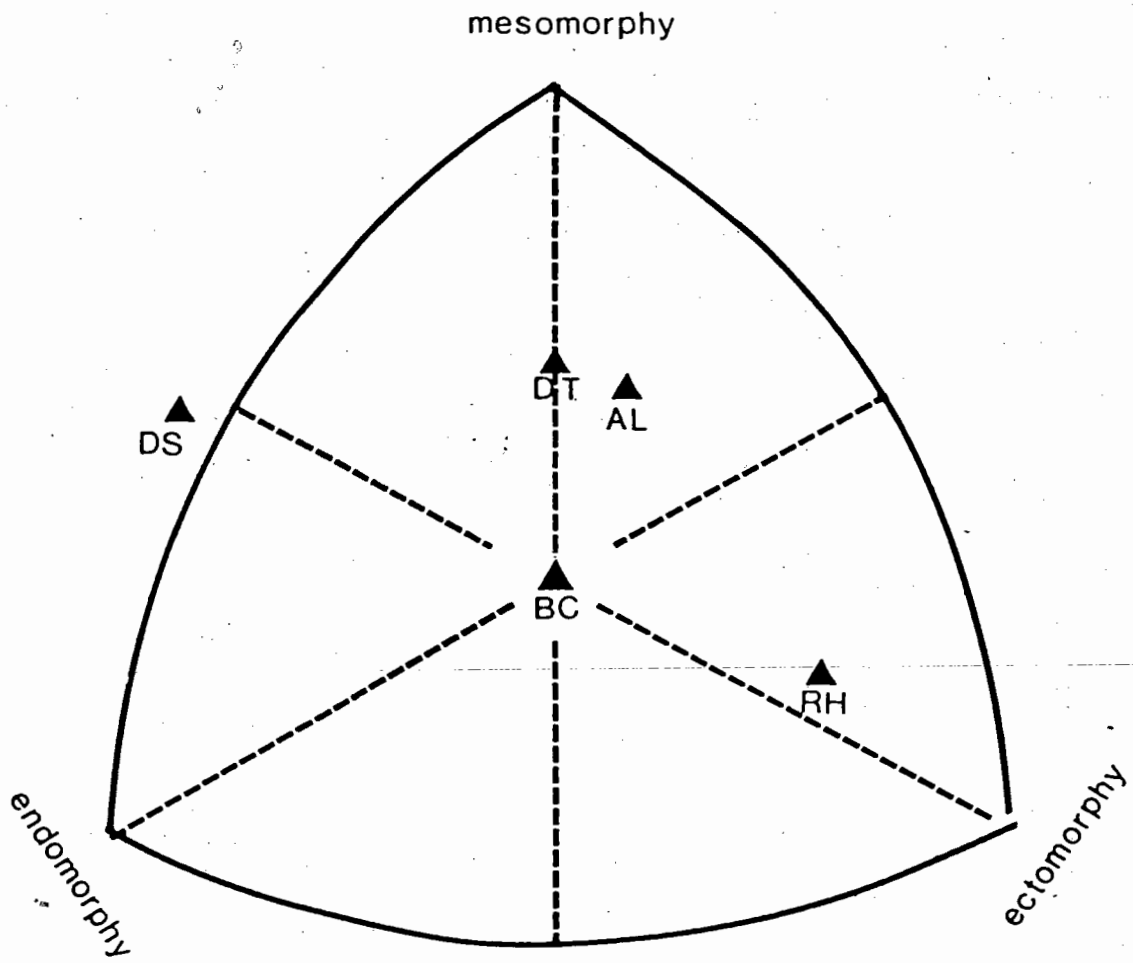
Experimental Paradigm

Each subject was required to participate in a total of six immersions. During each immersion, the water temperature was held constant at either 10°, 15°, or 20° C. The subjects were exposed to each water temperature on two occasions. On one occasion, the subjects inhaled humidified warm air (40° - 45° C), and on the other, the inhalate was normal room air (20° C).

Resting values of the physiological variables monitored were obtained in a five minute period preceding the immersion. The subjects then climbed into the water tank and sat with the water level up to their chin. Subjects remained immersed in water for one hour or until their rectal temperature dropped to 35° C.

Upon completion of the immersion, the subjects were assisted out of the tank, dried with a towel and placed in a sleeping bag for the rewarming period. Rewarming was monitored for 30 minutes, at which point the subject was disconnected from all the recording devices, the electrodes were removed and the subject was placed in a hot tub to complete the rewarming. This final rewarming in a hot tub was essential, as the sleeping bag rewarming did not bring the subjects' core temperature to normal levels and they still experienced muscle stiffness and fatigue after the 30 minutes of sleeping bag rewarming.

During the experimental procedure, data was collected at minute intervals with a HP 3497A Data Acquisition System

(Hewlett Packard) controlled by a HP 85 desktop computer
(Hewlett Packard). The acquisition of data during the experiment
is depicted diagramatically in Fig. 4.2. The collected data was
printed on a thermal printer built into the HP 85 and later
transferred into a data file on the main university computer,
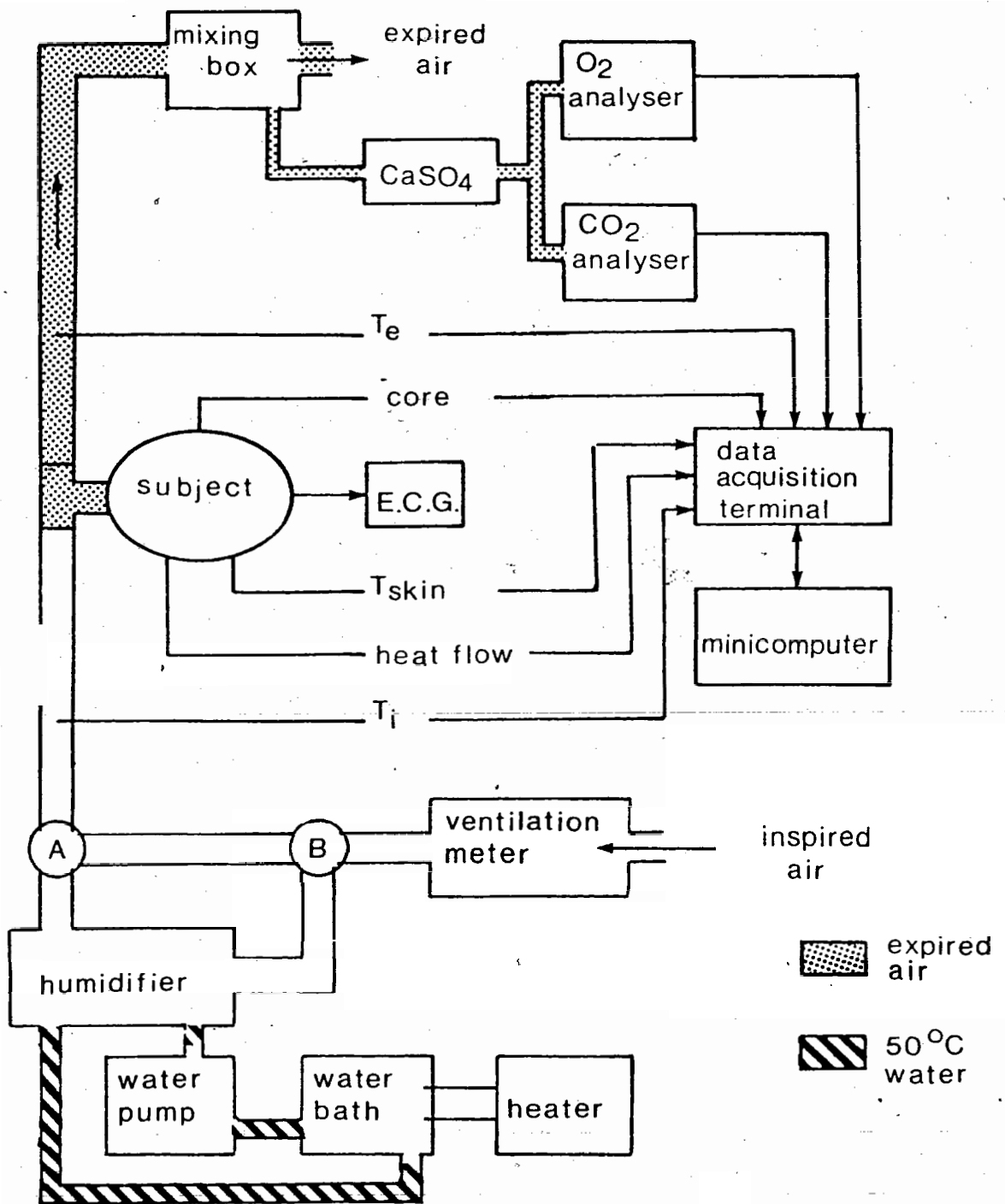IBM 4341, for further analysis.

Instrumentation

Immersion Tank

An immersion tank was constructed, having dimensions of .9
x .9 x 1.52 metres. The tank consisted of a steel frame with
sides of 1.8 cm. plywood. A vinyl liner was custom made for the
tank, which had a total volume of 1.215 cubic meters. The water
temperature in the immersion tank was maintained constant at
temperatures ranging from 10° to 20° C, by a constant flow
portable cooling unit (Blue M Electric Co., Blue Island, Ill.).
The water was continuously circulated by a Dynalflow power
filter capable of pumping 2730 litres of water per hour. A two
step aluminium frame was lowered into the tank at the onset of
each experiment, enabling the subjects to enter and exit the
tank. During the immersion, the frame provided seating for the
subjects.

Fig. 4.2 : Experimental arrangement.
Two way valves A and B could be arranged, so that the
subject was inhaling either air at room temperature or air
heated to $40^{\circ} - 45^{\circ}$ C and saturated with water vapour.

mixing box — expired air

O_2 analyser

$CaSO_4$

CO_2 analyser

T_e

core

subject

E.C.G.

T_{skin}

heat flow

T_i

data acquisition terminal

minicomputer

ventilation meter — inspired air

A

B

humidifier

water pump

water bath

heater

expired air

$50\,^{\circ}C$ water

To prevent deterioration of the water, the pH and chlorine level was continuously monitored and the water treated adequately, to maintain a ph of 7.2 and an appropriate chlorine level (1.0 p.p.m.).

Respiratory Gas Analysis

The evaluation of expired gas entailed measuring ventilation, temperature of inspired and expired gas, and the fraction of carbon dioxide and oxygen in the expired and inspired air. Inspired fractions of O_2, CO_2 and N_2 were determined prior to the onset of the experiment.

During the immersion, the inspiratory side of a two way valve was connected by Collins corrugated plastic tubing to a Parkinson Cowan Dry Gas Ventilation Meter (Parkinson Cowan, Chatham, Ont.). The expiratory side was connected similarly to a 17.78 x 31.75 x 21.59 cm. plexiglass mixing box. Mixed expired gas was sampled from the mixing box and analysed for CO_2 content by a Godarth Capnograph (Godarth Statham) and for O_2 content by an Applied Electrochemistry S-3A Oxygen Analyser (Applied Electrochemistry B.V.). The gas samples were drawn through a tube filled with dessicant (Drie-Rite), thereby extracting water vapour from the gas sample.

The experimental arrangement for the analysis of respiratory gas is illustrated in Fig. 4.2. This arrangement was used for the P.W.C. 170 tests, cold water immersions and

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rewarming periods. Such an arrangement enabled a series of experiments to be conducted, whereby the subject inhaled warm saturated air during immersion and rewarming. In these experiments, inhaled air was drawn through a humidifier before it reached the subject. The humidifier was essentially a mixing box, having identical dimensions of the mixing box described previously, insulated with 2 cm. neoprene. Water, which was previously heated in a water bath, was pumped to the interior top part of the mixing box. Within the mixing box, the warm water was pumped through a series of perforated plastic tubes, thus allowing the water to spray the entire interior of the mixing box; it then drained back to the water bath and was recirculated. In this manner, the air inside the mixing box was saturated with water vapour and heated to a specific temperature, which was dependent on the temperature of the water bath and was controlled by a Heto Denmark heater.

To prevent excessive cooling and condensation in the inspiratory tubing, between the mixing box and the mouthpiece, the Collins corrugated tubing was insulated with 2 cm. neoprene.

Heart Rate

For the P.W.C. 170 test, heart rate was recorded from three disposable pre-gelled electrodes (Harco Electronics Ltd., Winnipeg, Manitoba) placed in the CM5 position and an electrocardiogram was obtained using a Century SCC -1A E.C.G.

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recorder (Fukuda Denshi Co., Ltd.).

Electrocardiographic recordings during the immersion studies were obtained from two Beckman silver chloride miniature electrodes, placed laterally on the thorax (midchest, approximately at the 5th intercostal space). During the five minute pre-immersion rest period, the ground lead was placed on the right foot. Once the subject was immersed up to the neck in water, the ground lead was immersed in the tank, thereby grounding the subject.

Electrocardiograms were also obtainable from the esophageal probe, but these were used only for positioning of the probe prior to immersion (see Appendix II.).

Temperature Measurements

In experimental situations, it is crucial to be able to standardize measurement sites and accurately obtain temperature measurements of the core and shell.

1. Shell Temperature

The measurement of the temperature of the shell involves either measuring surface skin temperature, subcutaneous tissue temperature, or both. In the present study, surface skin temperature was measured at four sites:

a. arm - lateral aspect of upper arm

b. chest - right lateral midclavicular line at the third intercostal spacing.

c. thigh - anterior surface of the mid thigh

d. calf - upper lateral aspect of the calf.

Weighted mean skin temperature was calculated using the formula of Ramanathan (1964) :

$$Ts = .3 \times (Tarm + Tchest) + 0.2 \times (Tthigh + Tcalf) \quad ...(4.1)$$

Measurements of skin temperature were made with 36 gauge copper-constantan, T-type thermocouples (Omega Engineering Inc. Stamford, Ca.).

2. Core Temperature

Ideally the temperature of the core should be taken at the same anatomical location for all subjects and slight variations in the probe placement should not cause any significant changes in the temperature reading. Once the core temperature probe is inserted, a method of verifying the location of the probe is beneficial, so as to prevent any looping and unnatural bending of the catheter within the body cavity.

a. Tympanic Temperature

The location of the tympanic temperature probe is fairly easy to assess. The tympanic thermocouple was inserted in the aural cavity until it just touched the tympanum, at which point contact was perceived by the subject. The probe was then eased back approximately 1 mm. and taped into place. The aural cavity was then

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closed with cotton and water proof tape. Due to the rigidity of the probe ending and the short distance in the aural canal, the location of the probe could be assumed to be in the proximity of the tympanic membrane. To prevent damage occuring at the tympanic membrane, the thermocouple junction was protected by a soft ball of cotton.

b. Rectal Temperature

Rectal temperature was measured using a YSI 401 thermistor probe, inserted 10 cm. beyond the anus. The location of the tip of the rectal probe could not be verified other than by the actual length of probe inserted. Due to peristalsis of the alimentary canal, looping of the probe was not anticipated. The probe could not be checked for slippage continuously, during the immersion, however checks prior to and immediately after the immersion revealed that little or no change occurred in the depth of insertion.

c. Esophageal Temperature

The esophageal thermocouple temperature probe was constructed according to the suggestions made by Brengelmann (1981). During insertion the thermosensitive ending was connected to the positive electrode terminal of an electrocardiograph. The negative lead was connected to an electrode on the scapula. An electrocardiogram obtained from this arrangement enabled

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elctrocardiographic verification of the positioning of the thermosensitive tip within the esophagus, as suggested by Brengelmann et al. (1979). The probe was positioned at the atrial level.

Construction details of the probe as well as the methodology of the electrocardiographic verification of positioning is outlined in Appendix II.

Ventilation

Ventilation was measured on the inspiratory side of the two way valve, as shown in Fig. 4.2. In order to evaluate the accuracy of the ventilation meter, the experimental respiratory arrangement was connected to a respiratory simulator (Milne, 1978).

The simulator consisted of a pneumatically driven piston with a gearing mechanism producing a sinusoidal displacement of the piston. It was possible to vary the magnitude of the piston displacement, thus varying the stroke volume. Since the pulmonary simulator was connected to the experimental breathing arrangement, the volumes displaced by the piston represented a simulated ventilatory volume. Inspiratory circuits for both room temperature air and warm air breathing, as depicted in Fig. 4.2, were investigated to determine the accuracy of ventilatory measurements. The calibration arrangement is presented in Fig. 4.3.

Fig. 4.3 : Arrangement for calibration of Parkinson Cowan Dry
Gas Ventilation Meter. Respiratory simulator was connected
to A for simulation of experiments where the inhalate was
room temperature air and to B, for simulation of experiments
where heated air saturated with water vapour was inhaled.
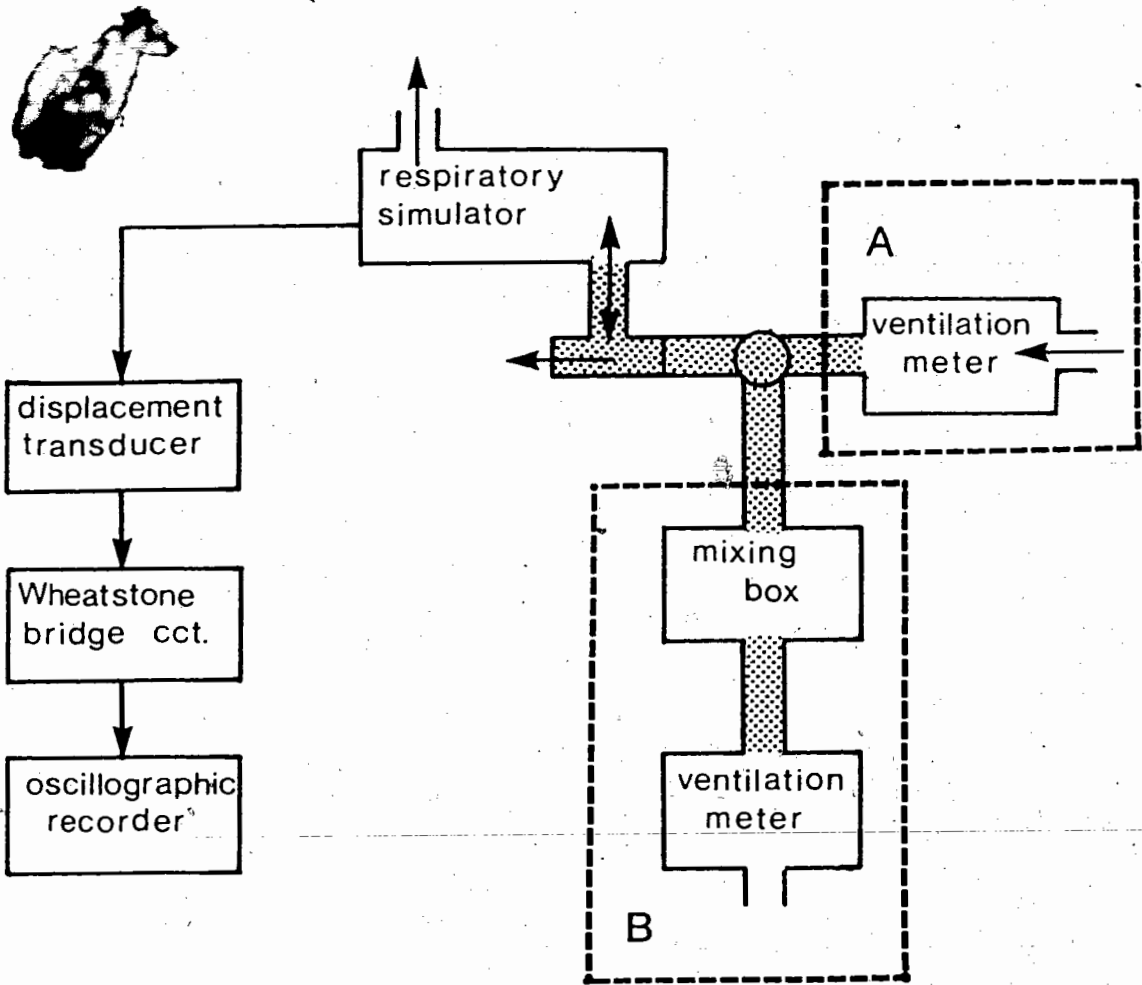
A – room temperature air

B – warm saturated air

Displacement of the piston was measured with a long stroke d.c./d.c. displacement transducer (S.E. type 353/150 mm; Intertechnology Ltd.) connected to the piston rod. The displacement transducer was connected through a Wheatstone bridge circuit and an HP 17401A Medium Gain D.C. Preamplifier to an HP 7404A Oscillographic Recorder (Hewlett Packard).

The volumes obtained by integrating the displacement of the piston and converting it to a volumetric measurement correlated well ($r = 0.955$) with volumes obtained by visual observation of the Parkinson Cowan Dry Gas Ventilation Meter (see Fig. 4.4).

Fig. 4.4 : Correlation of ventilatory volumes, as determined
    from the output of the displacement transducer connected to
    the piston of the respiratory simulator (see text), with
    values determined visually from the Parkinson Cowan Dry Gas
    Ventilation Meter. Symbols represent different tidal
    volumes, Vt (triangles: Vt = 1.0 liter; circles: Vt = 2.0
    liters). Closed symbols represent calibration of
    experimental arrangement where the respiratory simulator was
    connected to A (see Fig. 4.3) as opposed to circuit C,
    depicted by open symbols $(r^2=.955)$.

line of identity

Respiratory Simulator (l./min.)

Parkinson Cowan Ventilation Meter (l./min.)
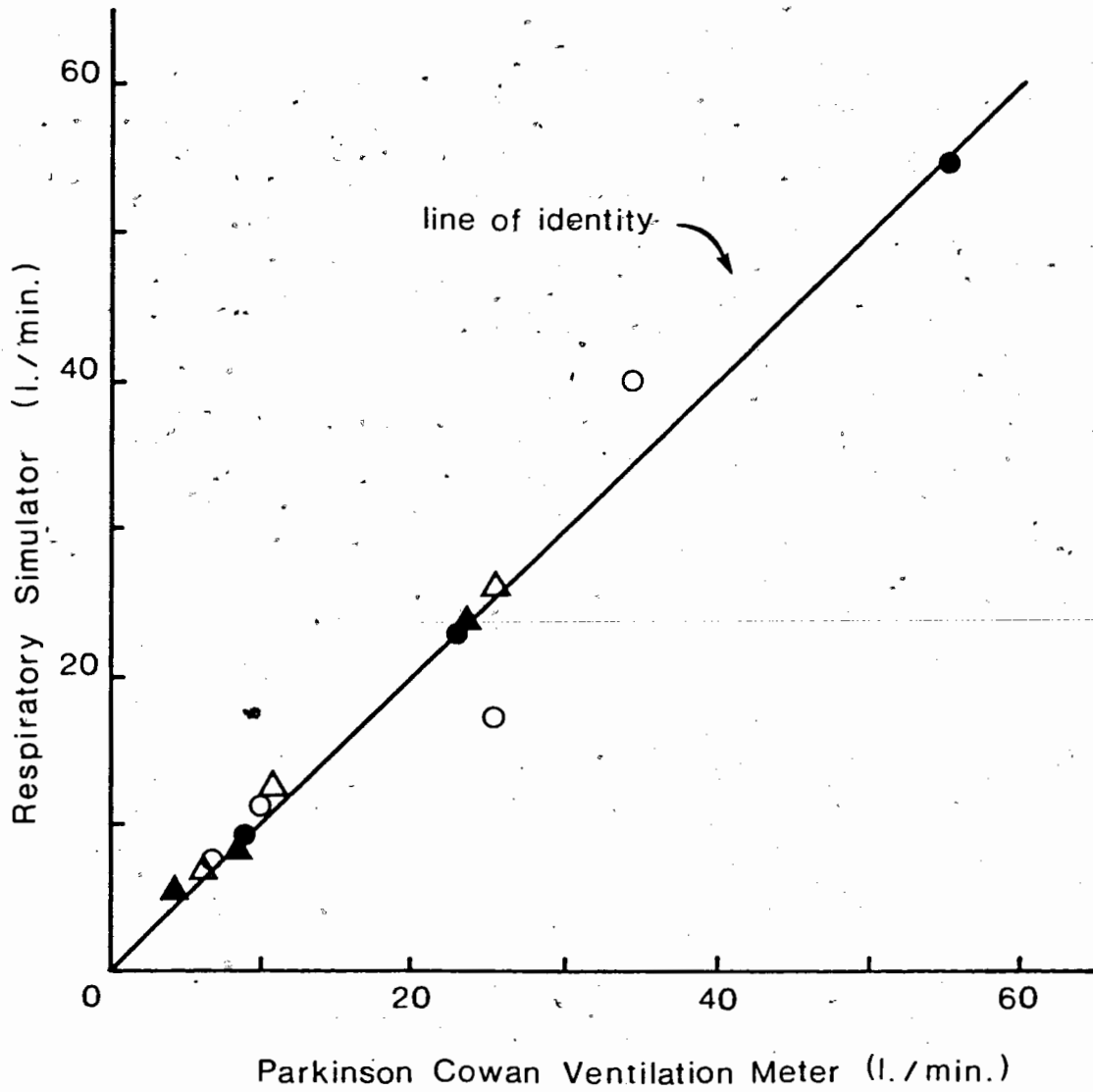
III. Results

In the following discussion of the results a specific notation will be used to denote a certain experiment. The label of an experiment will consist of the subject's initials (i.e.: AL, BC, DS, DT or RH), the temperature of the water (10°, 15° or 20° C) and whether the inhalate was at room temperature (N) or warmed and saturated with water vapor (W). BC10N would, in example, denote the experiment conducted on subject BC in 10° C water, while inhalaling air at room temperature, as depicted in Fig. 4.5.

Skin Temperature

In the immersion tank, subjects were instructed to assume a natural sitting position in the water. Nevertheless, subjects were observed occasionally to bring their upper arms closer to the side of the chest, thereby increasing the temperature at that site by covering the chest thermocouple with their upper arm. These instances can be observed on the mean skin temperature graphs as either fluctuations or quite pronounced rises in mean skin temperature. An example of such considerable changes in skin temperature is experiment DS10N (Fig. 4.6) between minutes 12 and 30 of the immersion period. The mean skin temperature, which has stabilized at approximately 12° C
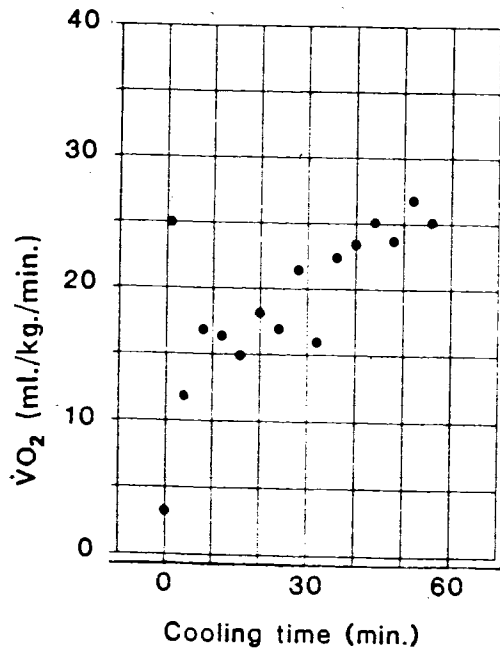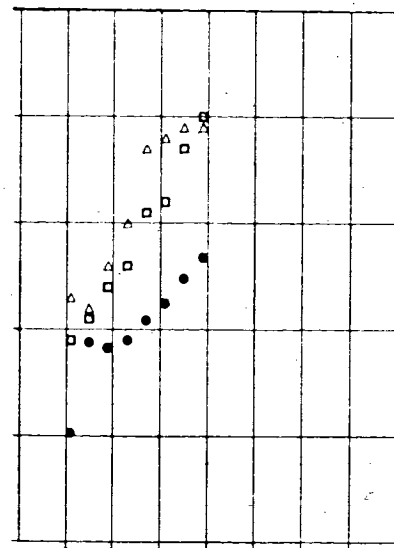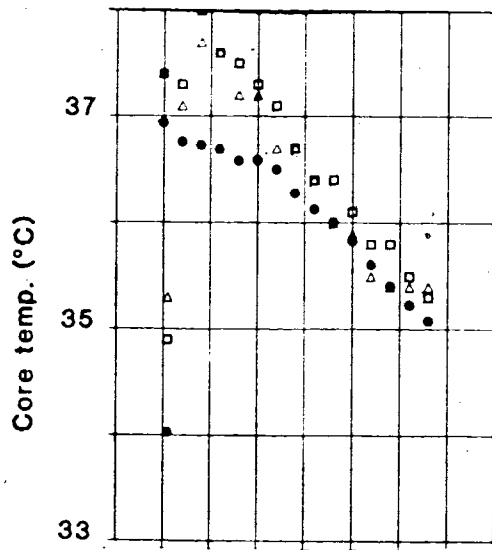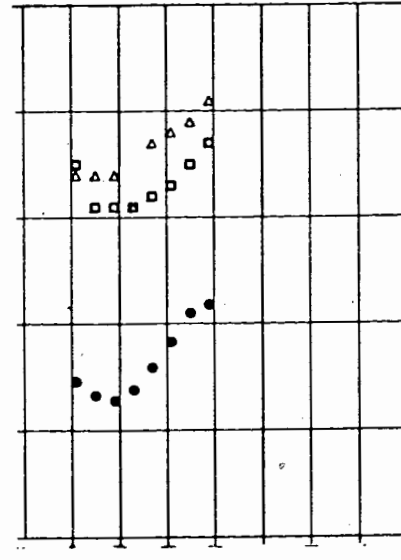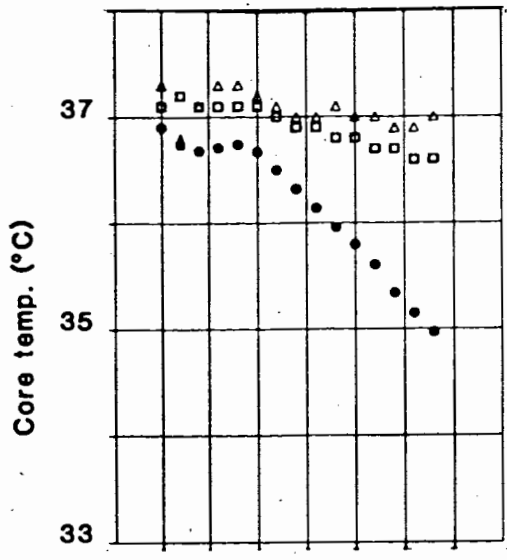
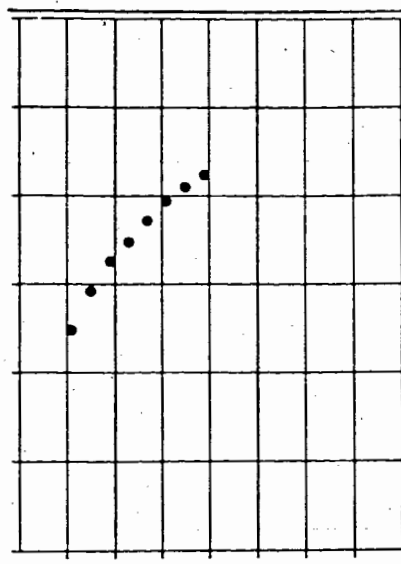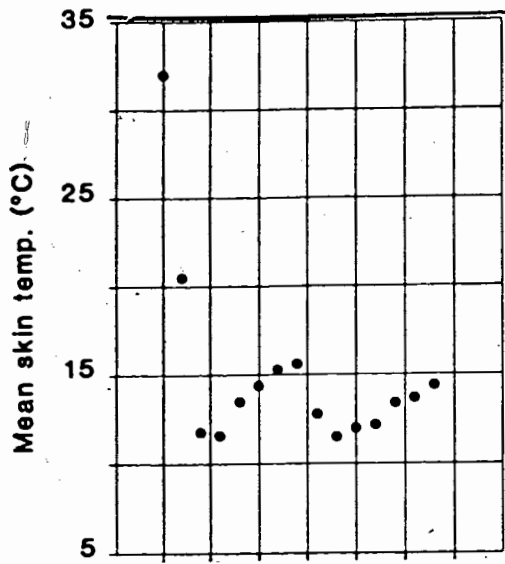Fig. 4.5 : Experiment BC10N

184b
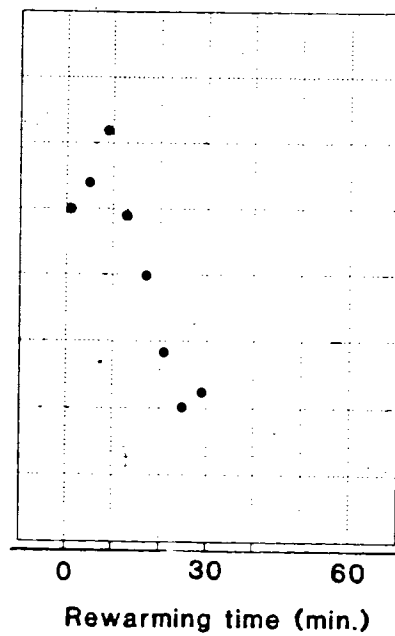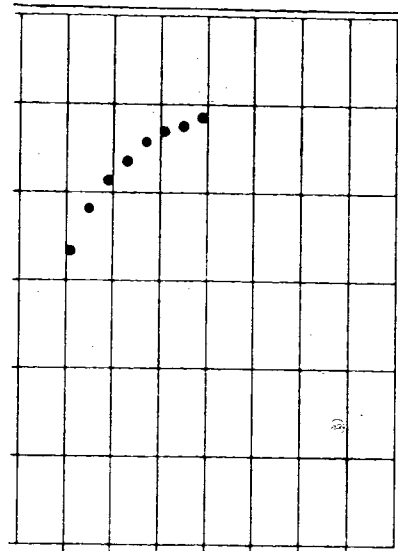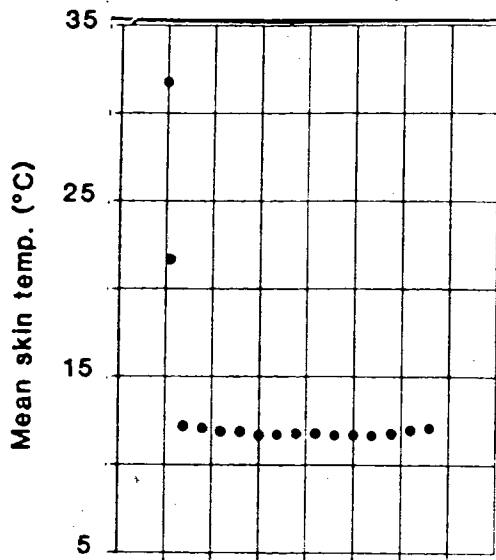
Fig. 4.6 : Experiment DS10N

185b
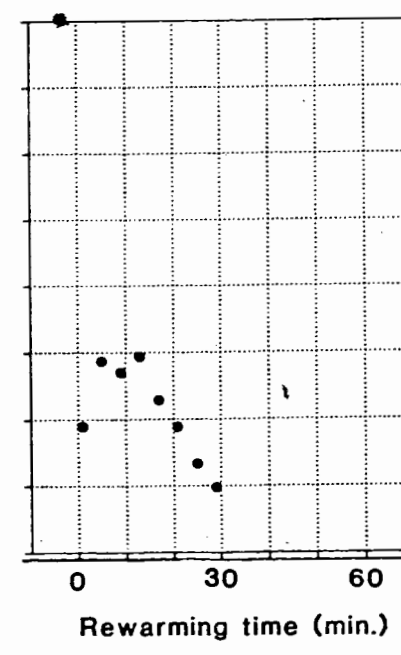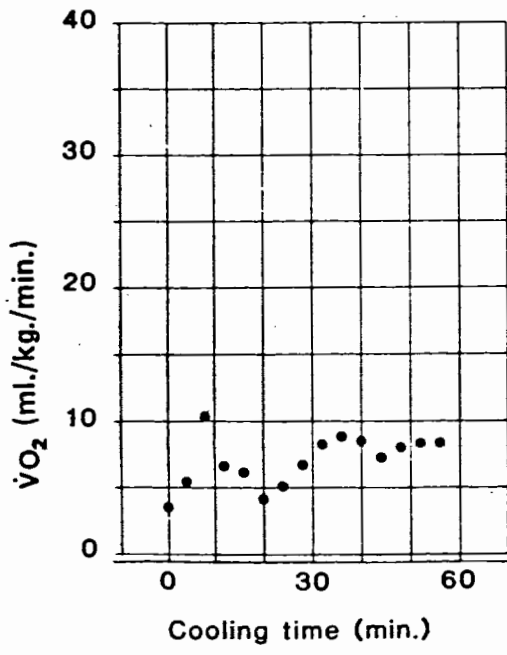
suddenly rises parabolically to 16° C. At that point, the subject was requested to keep his arms away from the chest, as evidenced by a subsequent fall in skin temperature. The later rise in skin temperature observed in this experiment, is again attributable to the subject's reluctance to expose the side of the chest and his urge to keep warm. Most subjects reported that by covering the side of the chest, they felt considerably warmer. Such examples on a minor scale can be observed in most experiments.

During the onset of immersion skin temperature decreased to steady state levels, slightly above water temperature, within five minutes. There was no observable difference in the time period required to achieve steady state between different water temperatures. For a given temperature of water, skin temperature stabilizes at similar levels when the subjects are inhaling warm air saturated with water vapour as when subjects are inhaling air at room temperature. Therefore, the peripheral vasoconstrictor response appeared to be unaffected by the central warm stimulus.

At the onset of rewarming, skin temperature rose parabolically to pre-immersion levels. The time required to reach pre-immersion values appeared to be independent of the temperature of the water in which the subject was immersed prior to the rewarming.

Fluctuations in mean skin temperature did not appear during rewarming, probably due to the uniform posture maintained by all

subjects in the sleeping bag and due to the development of a fairly stable microclimate in the sleeping bag.

Core Temperature

Some variability was noticed between temperature measurements obtained at the rectal, tympanic and esophageal sites, although the overall responses to cooling and rewarming appeared to be similar. The discrepancies in core temperature measurements at various sites, in the present study and studies reported in the literature, are discussed in Appendix III.

In cases of rapid core cooling, such as RH1ON (Fig. 4.7), the temperature responses of the three sites overlapped, giving core temperature responses of identical magnitude. In twelve of the thirty experiments, esophageal temperature was maintained at levels higher than that of tympanic and rectal temperature. Examples of this are experiments DT2ON (Fig. 4.8), AL1OW (Fig. 4.9) and BC15W (Fig. 4.10).

The response of tympanic temperature in ten of the immersion trials was lower than esophageal and rectal temperatures, as seen in experiments DT2ON (Fig. 4.8), AL1OW (Fig. 4.9) and BC15W (Fig. 4.10). In two experiments the tympanic temperature was observed to be 3° C lower than rectal temperature. Insufficient insulation of the auditory canal may have caused these observations.

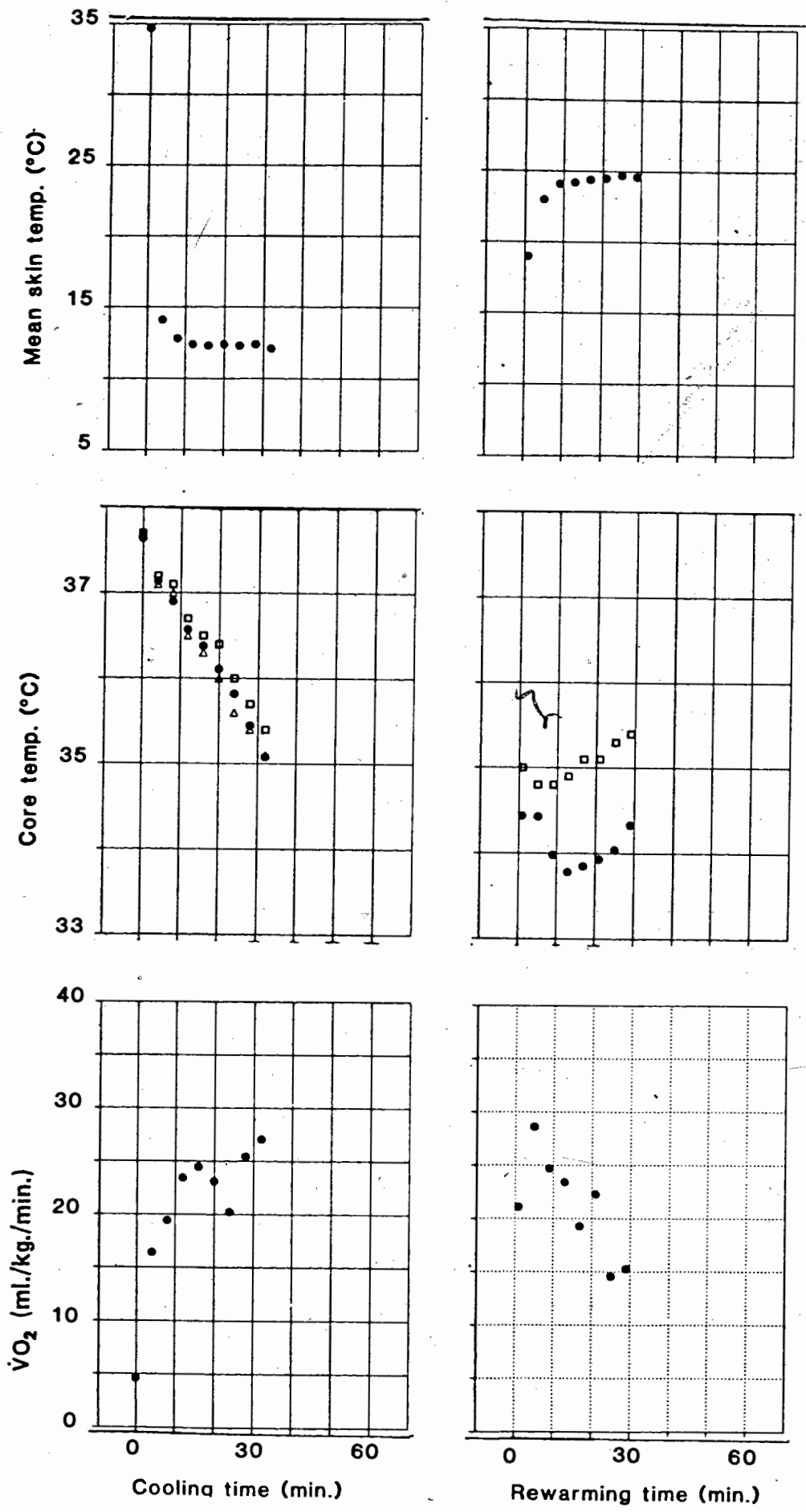Fig. 4.7 : Experiment RH10N

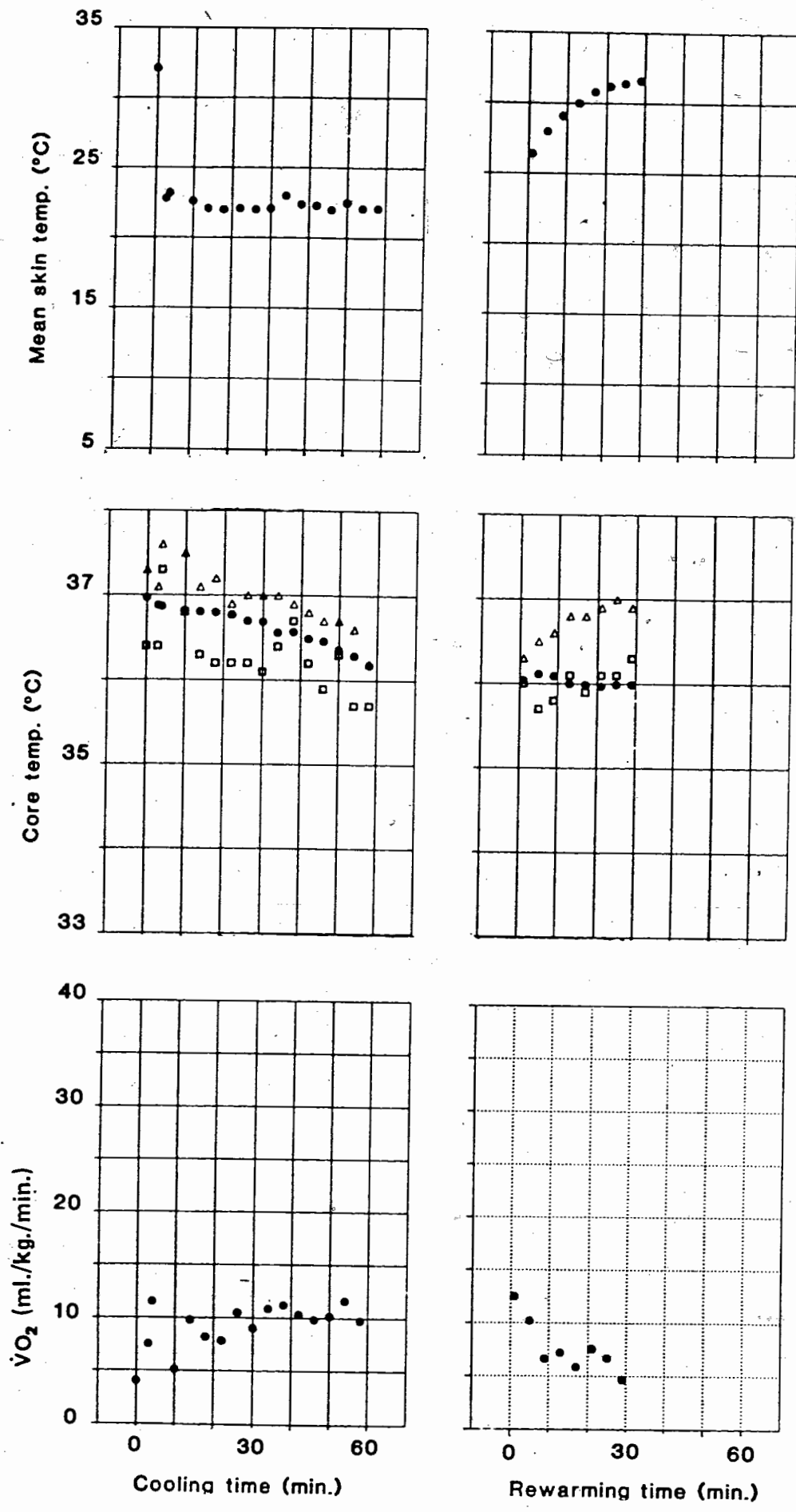188b

Fig. 4.8 : Experiment DT20N
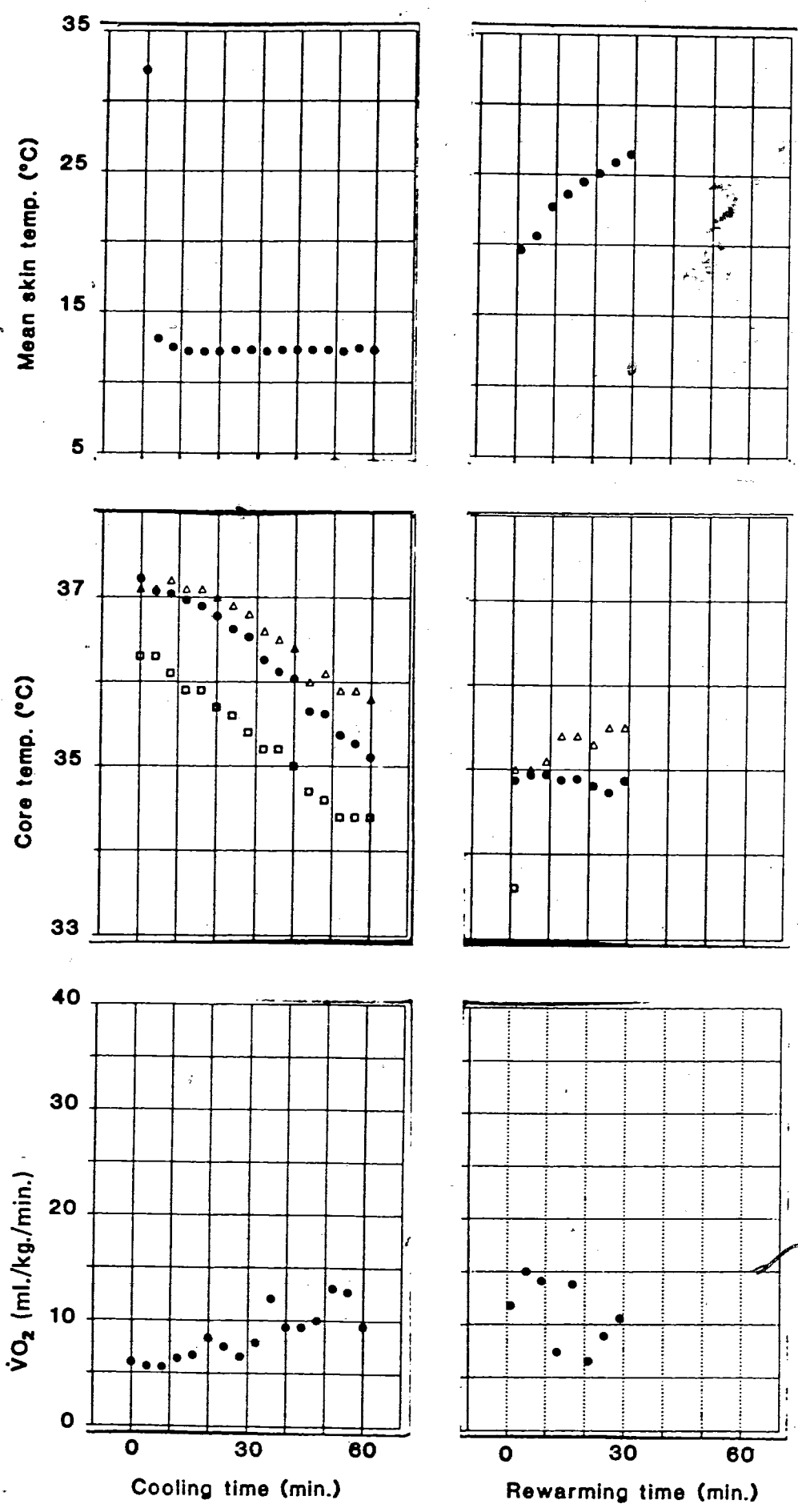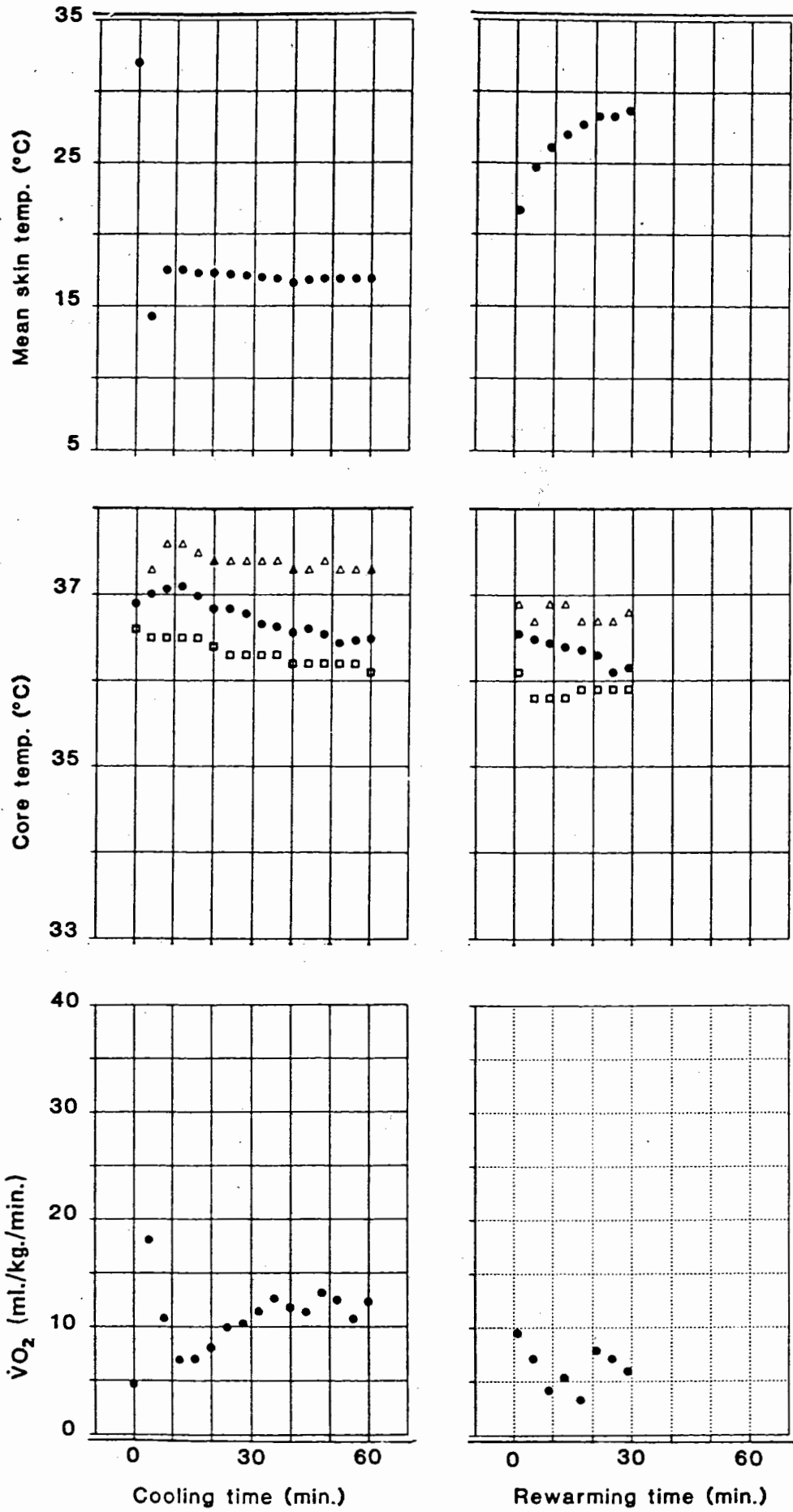
Fig. 4.9 : Experiment AL10W

Fig. 4.10 : Experiment BC15W

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Esophageal temperature was either higher or equal to rectal temperature in all experiments, except RH15N (Fig. 4.11), where esophageal temperature exhibited the greatest cooling rate. As indicated by Fig.1, subject RH had a high ectomorphic component, suggesting a more pronounced exposure of the thoracic region.

In water at 10° C, inhaling warm saturated air decreased the cooling rate in most subject, the exceptions being subject RH, where the cooling rate was increased.

The differences in core cooling rate between normal air breathing and warm air breathing were not as evident for immersions in 15° C and 20° C water. As seen from Table 4.2 there is considerable variability in individual responses. The significance of these responses are discussed further in Appendix III.

On rewarming, esophageal temperature recovered to pre-immersion levels faster than the other two core temperature measures and exhibited the least amount of afterdrop. In all cases, the extent of the afterdrop in core temperature was lessened with inhalation rewarming.

At the onset of immersion, three distinct core temperature responses were observed :

1. Immediate cooling of core temperature, as in experiments DT20N (Fig. 4.8) and RH15N (Fig. 4.11). In most cases the cooling rate consisted of two components. In the initial stages of immersion, the cooling rate was fairly slow but as immersion progressed, the cooling rate increased. The
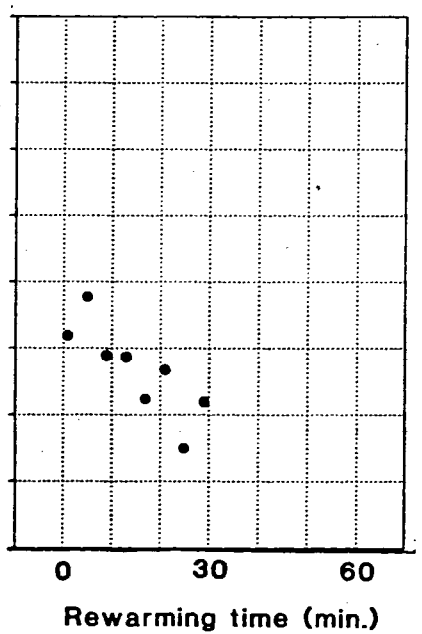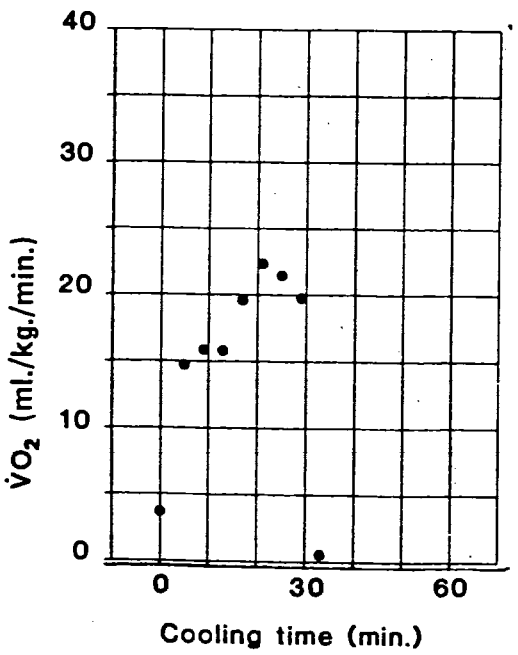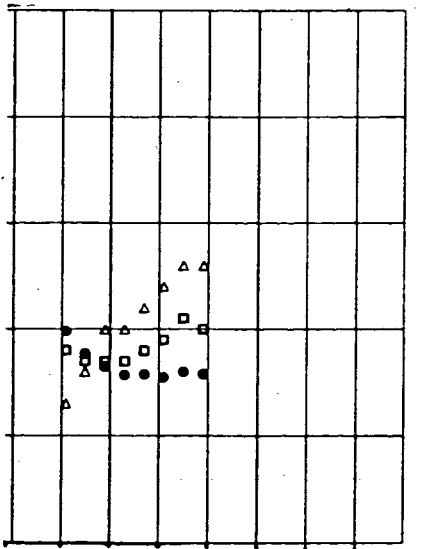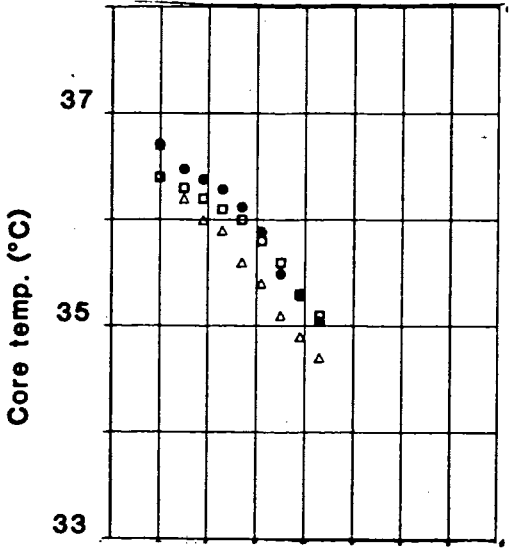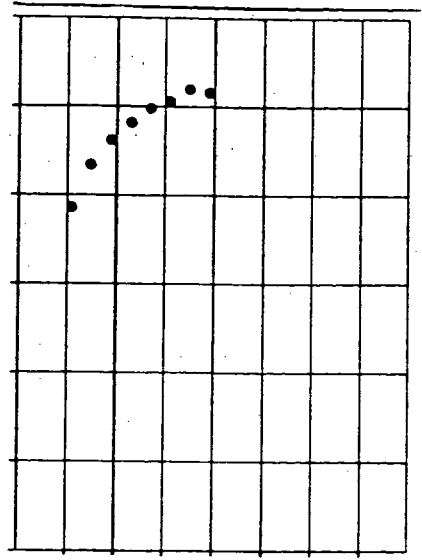
192

Fig. 4.11 : Experiment RH15N
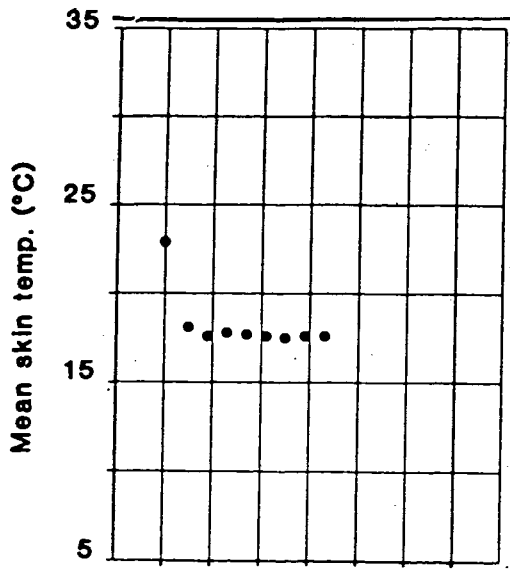
Table 4.2 : Cooling rate of subjects during different
     experimental conditions.

Core cooling rates (°C/minute)

Water temp. (°C)	Subj.	N ΔTr/Δt	N ΔTe/Δt	N ΔTt/Δt	W ΔTr/Δt	W ΔTe/Δt	W ΔTt/Δt
10	AL	.0392	.0316	.0316	.0352	.0217	.0317
	BC	.0336	.0356	.0356	.0162	.0086	.0121
	DS	.0345	.0054	.0089	*	.0033	.0_
	DT	.0485	.0235	.0235	.0225	.0083	.033
	RH	.0812	.0788	.0727	.0788	.0833	.033
15	AL	.0393	.0122	.0224	.0208	.0117	.0167
	BC	.0035	.0283	.005	.0068	.0	.0083
	DS	.0188	−.005	−.003	.0018	.0017	.0
	DT	.0131	.0049	−.0016	.0112	.0017	.005
	RH	.0506	.0606	.0394	.0842	.0526	.0316
20	AL	*	.0133	.01	.0153	.0083	.0117
	BC	.0053	*	.0067	.0095	−.0017	.0067
	DS	.0159	.0035	.0035	.0067	.005	.0067
	DT	.0138	.0131	.0131	.0132	.0083	.01
	RH	.048	.0433	.0233	.0312	.02	.015

N — denotes experiments where the inhalate was air at room temperature .

W — denotes experiments where the inhalate was warm air (40° – 45° C) saturated with water vapour.

ΔTr — change in rectal temperature over the cooling period (Δt).

ΔTe — change in esophageal temperature over the cooling period (Δt).

ΔTt — change in tympanic temperature over the cooling period (Δt).

* — probe slipped

exception was subject RH, whose cooling rate was high at the onset of immersion and remained fairly constant until removed from the cold water.

2. In some cases, core temperature was maintained at normal levels for varying periods of time. Thereafter the core temperature began to drop steadily, as observed in experiment DS15N (Fig. 4.12).

3. Occasionally, the fall in core temperature was preceded by a slight rise in core temperature, above pre-immersion values. Such a response is probably due to a combination of intense vasoconstriction and increased shivering thermogenesis, thereby increasing core heat content for a short period at the onset of immersion, as seen in BC15W (Fig. 4.10) and DS15W (Fig. 4.13).

Shivering Thermogenesis

The thermogenic response, indicated by elevated levels of metabolic rate, consisted of two major components. At the onset of immersion, there was a rapid elevation in oxygen consumption. In general, the peak of the rapid metabolic response was attained within the first minutes of immersion. Following the peak response, metabolic rate decayed to levels slightly above pre-immersion values and subsequently began to rise in a parabolic fashion. This latter response constituted the second component, having a much slower response time.
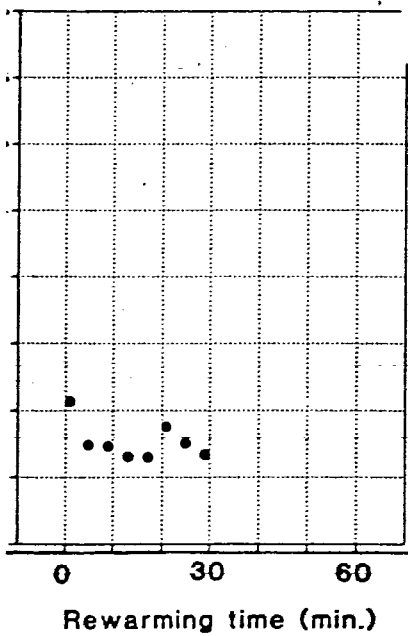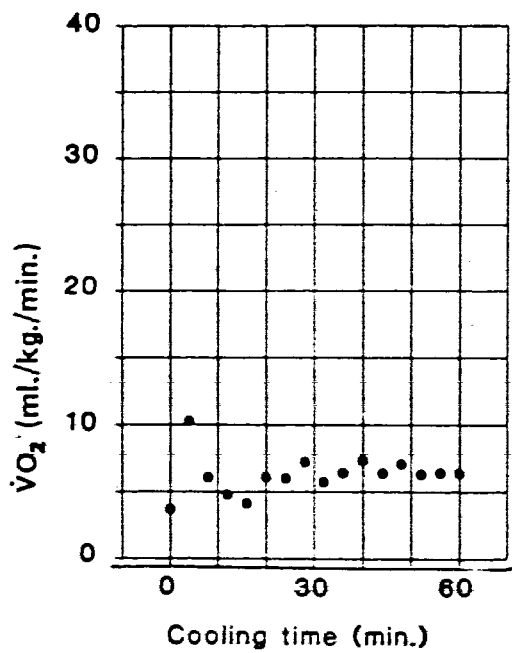
Fig. 4.12 : Experiment DS15N

196b
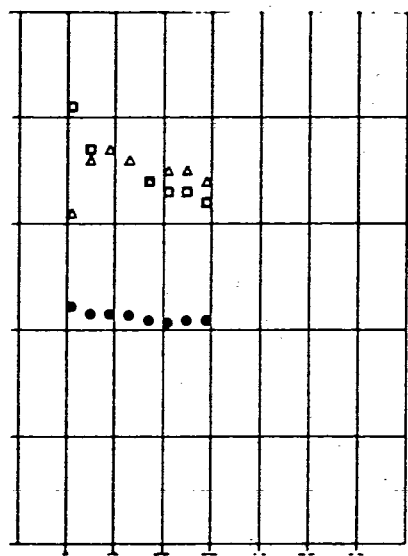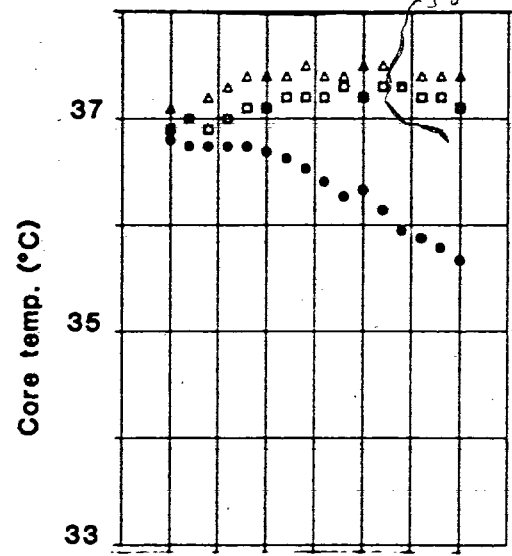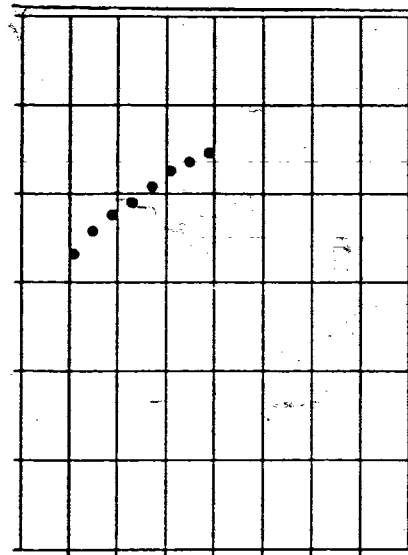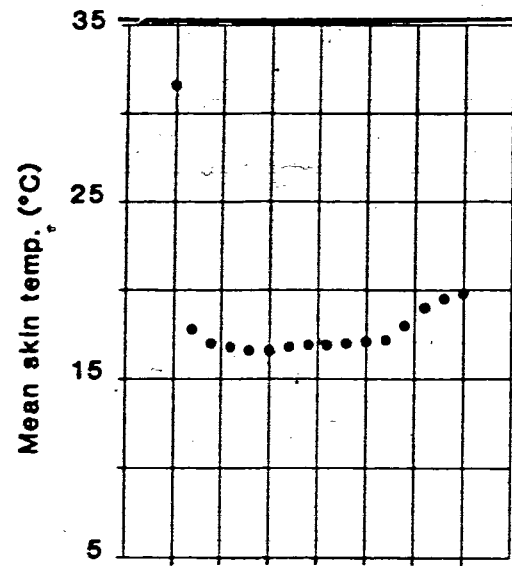
Fig. 4.13 : Experiment DS15W

197b
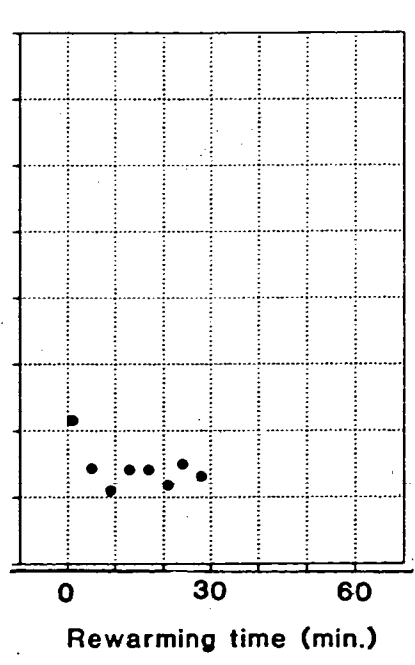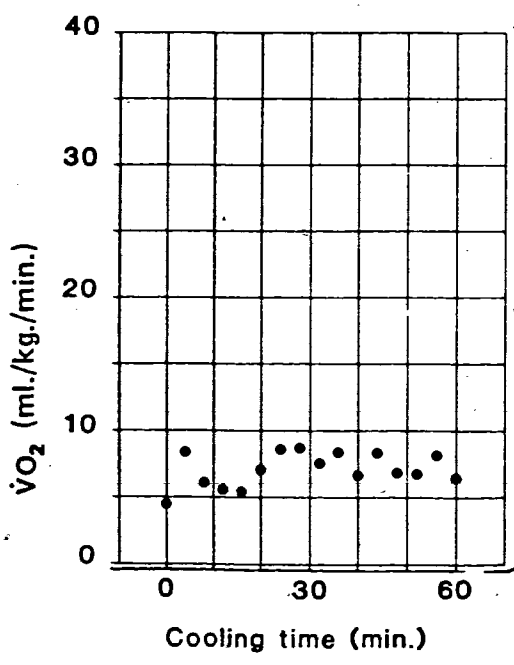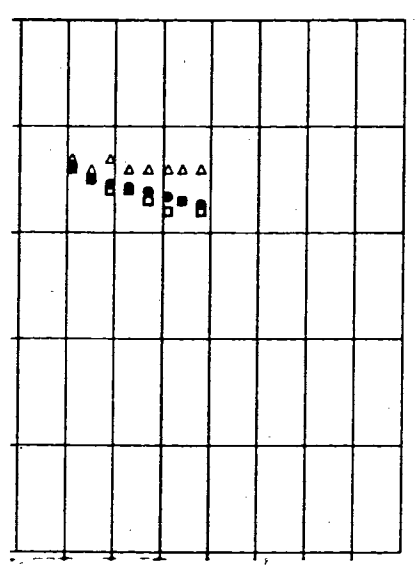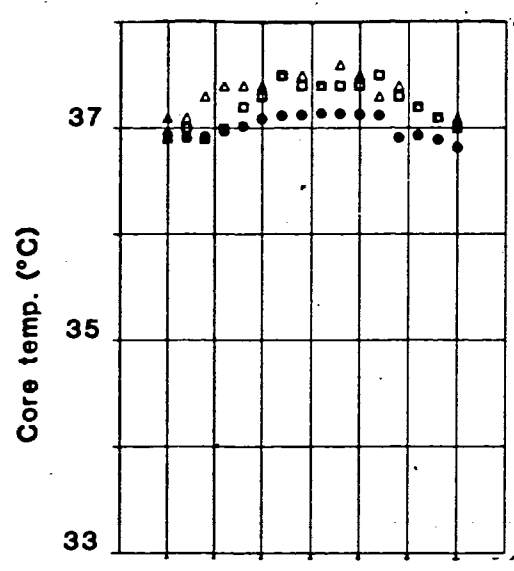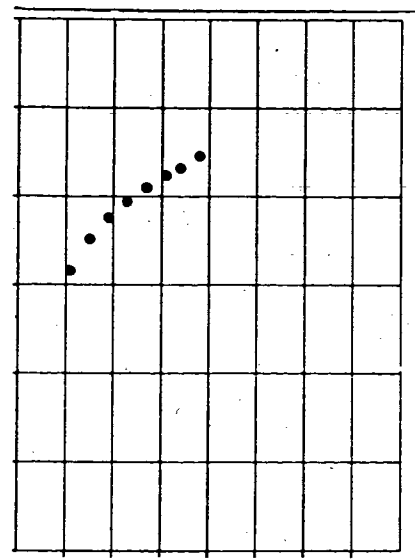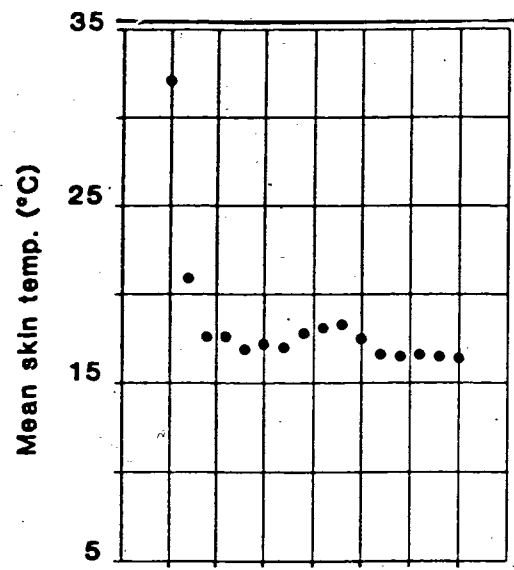
Comparing the peak values of the fast metabolic component, for the three water temperatures (Table 4.3), it can be observed that the peak values are greater for large drops in skin temperature. In similar water temperature, it is evident that the metabolic overshoot is somewhat influenced by core temperature. During the warm air breathing trials, the peak value of the fast component is lower than when breathing room temperature air.

It can be seen from Table 4.4, that the response of the slow component is influenced mainly by core temperature. Comparing the end immersion values of metabolic rate for normal air and warm air breathing, it seems that metabolic rate is substantially lower when respiratory heat is being delivered to the core. A comparison of the metabolic response at identical rectal temperatures and different skin temperatures indicates that skin temperature is also a dominant factor. For a given core temperature, the metabolic rate is higher at lower skin temperatures. For example, at a rectal temperature of 36° C, subject RH has a metabolic rate of 24, 22 and 17 ml.O2/min/kg at skin temperatures of 12.5° (Fig. 4.7), 17.5° (Fig. 4.11) and 22.5° C (Fig. 4.14), respectively. However, it is difficult to differentiate between the influence of steady state skin temperature and core cooling rate in the above example. The difference in thermogenesis observed at several levels of skin temperature is a resultant effect of static skin and dynamic core temperature.

Table 4.3 : Characteristics of the 'fast' component of the thermogenic response.

Water temp. (°C)	Subj.	N — Inhalate is room temperature air.			W — Inhalate is warm air saturated with water vapour.		
		Resting VO$_2$ (ml.O$_2$/kg./min.)	Peak VO$_2$ at onset of immersion (ml.O$_2$/kg./min.)	Time to peak VO$_2$ (min.)	Resting VO$_2$ (ml.O$_2$/kg./min.)	Peak VO$_2$ at onset of immersion (ml.O$_2$/kg./min.)	Time to peak VO$_2$ (min.)
10	AL	6.1	13.9	3	6.0	16.9	1
	BC	3.3	18.1	6	2.3	17.9	1
	DS	3.5	19.0	2	4.1	17.3	1
	DT	6.1	23.6	3	3.7	10.3	1
	RH	4.6	21.8	1	4.6	16.2	1
15	AL	3.4	6.9	1	5.7	11.5	2
	BC	4.7	26.7	2	4.7	18.9	2
	DS	2.9	14.4	2	4.5	10.1	1
	DT	2.7	18.9	6	4.6	17.3	2
	RH	3.7	19.3	1	3.1	10.2	1
20	AL	3.4	8.5	1	6.4	12.0	1
	BC	2.2	19.3	1	3.7	13.4	1
	DS	4.5	8.7	1	2.5	6.2	1
	DT	3.3	18.9	5	3.9	9.7	1
	RH	4.4	20.7	1	*	7.7	1

VO$_2$ - oxygen consumption

* - resting oxygen consumption was not determined prior to immersion

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Table 4.4 : Characteristics of the "slow" component of the
thermogenic response.

| | | | N | | | | | | W | | | |
Water temp. (°C)	Subj.	Δt (min.)	Tr (°C)	Te (°C)	Tt (°C)	Metabolic rate (ml. O$_2$/kg./min.)		Δt (min.)	Tr (°C)	Te (°C)	Tt (°C)	Metabolic rate (ml. O$_2$/kg./min.)
10	AL	38	34.99	35.7	35.1	12.8		60	35.11	35.8	34.3	10.7
	BC	59	34.96	35.3	35.3	24.4		58	36.04	36.8	36.2	19.9
	DS	56	34.97	37.0	36.6	7.6		60	*	36.8	36.7	6.6
	DT	34	34.97	36.1	35.9	26.8		60	35.83	36.9	36.1	18.0
	RH	33	34.96	35.1	35.3	25.5		24	35.01	35.6	35.9	18.9
15	AL	49	34.96	36.6	34.8	13.4		60	35.47	36.2	35.0	11.8
	BC	60	36.7	35.5	36.7	13.4		60	36.49	37.3	36.1	11.2
	DS	60	35.67	37.4	37.1	6.6		60	36.82	37.1	37.0	7.1
	DT	61	36.16	37.1	37.0	22.9		60	36.52	36.9	36.0	18.4
	RH	33	35.04	34.7	35.1	22.3		19	35.07	35.9	35.6	19.2
20	AL	60	*	36.4	35.8	7.5		60	35.84	36.5	35.4	8.4
	BC	60	36.6	35.2	36.6	12.2		60	36.49	37.4	36.8	8.1
	DS	58	35.67	36.7	36.6	5.7		60	36.6	36.7	36.5	3.7
	DT	61	36.13	36.5	35.6	12.0		60	36.05	36.6	35.3	11.4
	RH	30	35.06	35.6	35.8	18.3		60	35.15	35.8	35.8	16.8

N – denotes experiments where the inhalate was room temperature air.

W – denotes experiments where the inhalate was warm air saturated with water vapour.

Δt – period of immersion in minutes.

* – thermosensitive probe slipped

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Fig. 4.14 : Experiment RH2ON

35 ‑‑

Mean skin temp. (°C)

25

15

5

Core temp. (°C)

37

35

33

V̇O₂ (ml./kg./min.)

40

30

20

10

0

0   30   60
Cooling time (min.)

0   30   60
Rewarming time (min.)

201b
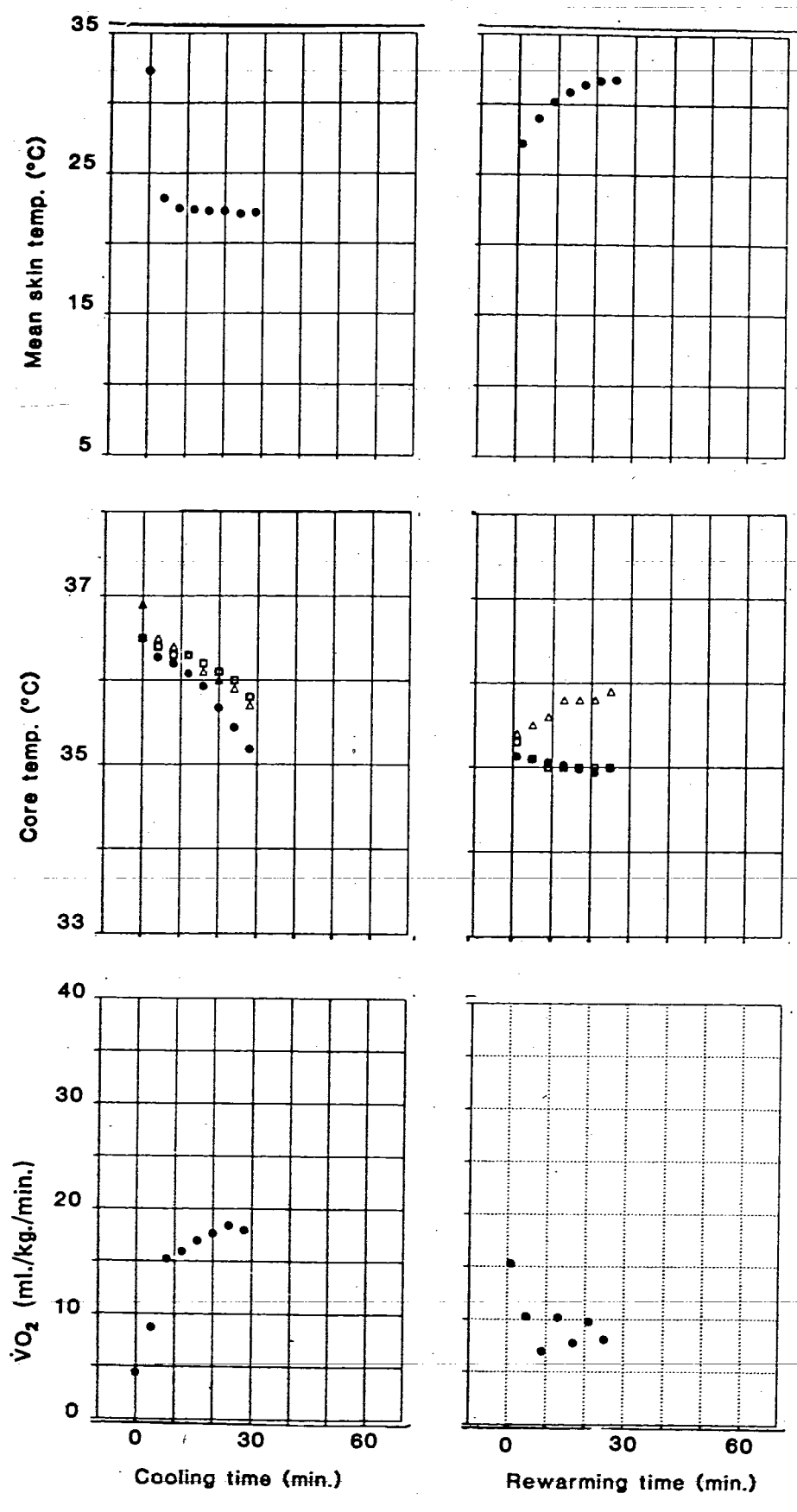
Fig. 4.15 : Experiment RH20W
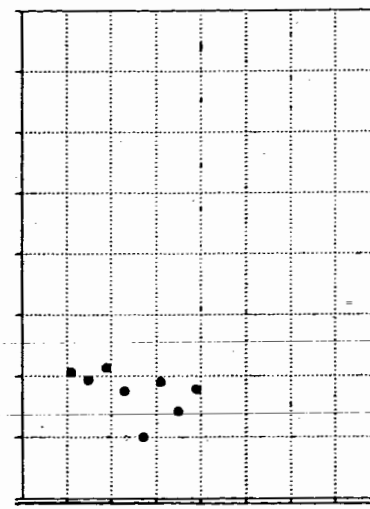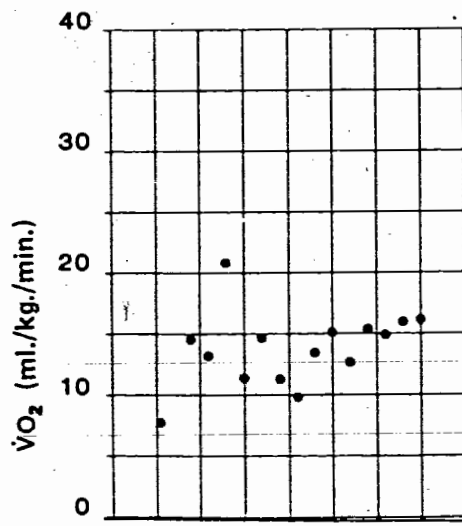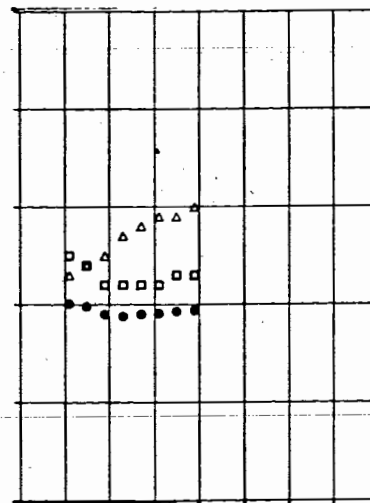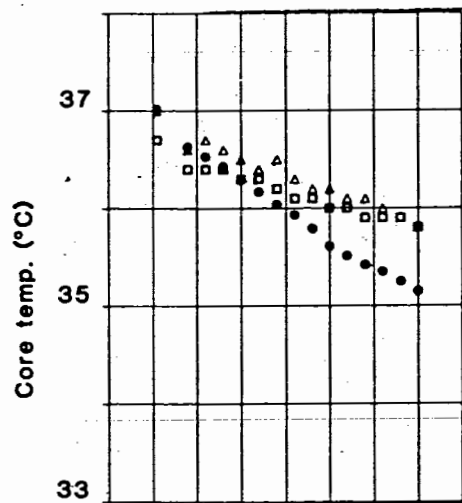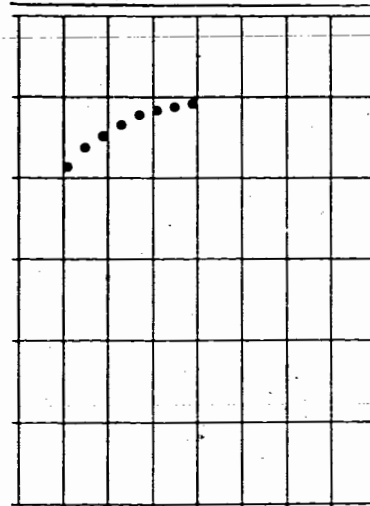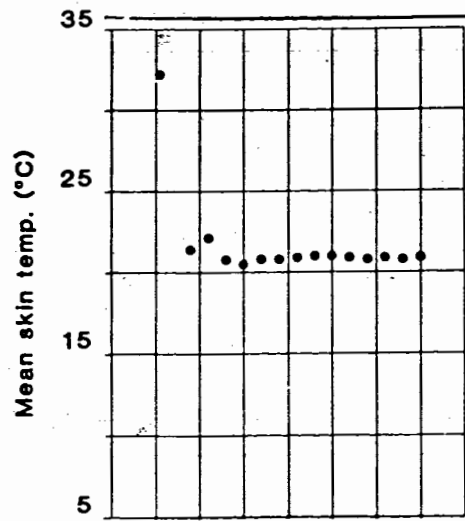
In cases of rapid core cooling the fast metabolic component associated with the rate of change of skin temperature is not evident, as metabolic rate rises rapidly. Examples of this are RH1ON (Fig. 4.7) and RH15N (Fig. 4.11). Some subjects, did not exhibit the metabolic overshoot and had a small overall metabolic response, despite a drop in skin temperature (DT20N in Fig. 4.8 and AL1OW in Fig. 4.9 are examples of this response).

Upon rewarming, two typical responses in metabolic rate become apparent:

1. metabolic rate may increase the above end immersion levels, before decaying towards resting levels. Examples of this type of response are observed in experiments AL1OW (Fig. 4.9), DS15N (Fig. 4.12) and RH1ON (Fig. 4.7).

2. metabolic rate is maintained at end immersion values for a short period, before decaying towards resting values, as in experiments BC15W (Fig. 4.10), DS15N (Fig. 4.12) and RH15N (Fig. 4.11).

The metabolic overshoot during rewarming was greatest following immersion in 10° C water and almost negligible following immersion in 20° C water. In experiments with inhalation rewarming, the metabolic overshoot during rewarming was lower than for passive rewarming in a sleeping bag. Since the recovery of skin temperature to pre-immersion levels is similar, for passive compared to active core rewarming, it is

unlikely that it is a dominant factor in the rewarming fast metabolic component. In comparison, there is a significant difference in the core recovery rate during rewarming. The magnitude of the core temperature afterdrop at the onset of rewarming is substantially greater during passive rewarming in a sleeping bag. On a time scale, the rewarming metabolic overshoot coincides with the core temperature afterdrop. Although skin temperature recovery rate is similar during both methods of rewarming, it should not be regarded as having a negligible affect on the metabolic overshoot observed. The skin temperature is passing through a thermal zone of maximum cold receptor sensitivity ($T = 20^{\circ} - 30^{\circ}$ C). The combined affect of the above peripheral factors may contribute substantially to the rewarming overshoot in thermogenesis.

IV. Discussion

The thermogenic response to cold water immersion consists of two components: a fast and slow component. The fast component is represented by an immediate overshoot in metabolic rate, coinciding with the onset of immersion. The peak of this metabolic overshoot occurs within the initial ten minutes of immersion and often within the first five minutes. Following the peak of the fast component, metabolic rate decays to a lower level, yet slightly higher than resting values. Similar overshoots in oxygen uptake have previously been reported by Benzinger (1969) and Hayward et al. (1977). Benzinger observed increases in oxygen consumption during immersion. The lower the water temperature in the bath, the greater the peaks in oxygen consumption. His findings were that 28°, 25.2° and 22° C water temperature induced metabolic peaks of increasing magnitude and duration; the peaks he observed were of the order of 390, 450 and 600 c.c. of oxygen consumed per minute, respectively. Following the fast metabolic component, metabolic rate stabilized at levels higher than resting.

Hayward et al. (1977) observed a similar component in their averaged data of all subjects immersed in 10° C water. The average metabolic overshoot observed was 3 W/kg. (equivalent to 2.42 l/min for a 75 kg man), the peak of which occurs within the first three minutes of immersion.

The present results confirm the findings of Benzinger (1969) albeit in a lower temperature zone. The fast component increases in magnitude as lower temperatures of water are used in the bath (20°, 15° and 10° C).

The response of the fast component varies among subjects. Subject AL, for example, did not exhibit violent shivering during immersion, this is reflected by the poor metabolic response during the immersion. An isolated case is similarly subject RH, an extreme ectomorph. Since his cooling rate was very rapid and instantaneous with the onset of immersion, the fast component is no doubt masked by his intense overall metabolic response. Such individuality in subject response is not reflected in the data of Hayward et al. (1977).

Benzinger (1969) suggests that the fast component is a result of skin cold receptor stimulation. It is reasonable to exclude core cold receptors, as in most cases where the overshoot is observed, core temperature is still at pre-immersion levels.

If the metabolic response is a result of cold receptor activity, then the response of cold sensitive fibres should be somewhat similar. Indeed, the response of a single cold receptor fiber to a step decrease in temperature is an instantaneous increase in firing frequency. Once peak firing rate has been reached, the number of impulses per second decreases to a steady state level, dependent upon the new adaptive temperature (Zotterman, 1953; Hensel, 1982). Kenshalo and Duclaux (1977)

have also observed that the magnitude of the overshoot in firing frequency increases with increasing cooling rate of the receptor and with greater steps in temperature change.

Assuming a close relationship between skin cold receptor activity and thermogenesis, the present results of the fast component can be adequately explained on the basis of the findings of Kenshalo and Duclaux (1977). Immersions in water at 20°, 15° and 10° C, respectively impose progressively greater step changes in temperature on the skin cold receptors and also induce greater cooling rates of the skin. The concomitant overshoots in firing frequency would therefore be progressively greater in magnitude for the 20°, 15° and 10° C water, respectively, resulting in greater fast components of the metabolic rate at lower water temperatures. Similarly, as cold receptor frequency decays to a new level proportional to the new peripheral cold stimulus, the decay of the fast component corresponds to the stabilization of skin temperature, slightly above that of the water temperature.

With the completion of the fast component, the second or 'slow' component becomes dominant, gradually elevating metabolic rate. The onset of the second component coincides in most cases shown, with the gradual cooling of the inner core, as observed from rectal, esophageal and tympanic measurements. Accepting the existence of cold sensitive structures within the abdomen and intestines, as suggested by Rawson and Quick (1971, 1972), within the spinal cord (Simon et al., 1965; Simon and Iriki,

1970), medulla and thalamus (Poulos and Molt, 1976), the second component of the thermogenic response may be attributed to increased activity of core cold receptors. According to Benzinger (1969, 1970), there exists a central warm inhibition of thermogenesis; regardless of the peripheral cold stimulus, the metabolic rate will not increase until the core temperature falls below a certain 'set-point' temperature value, suggested to be 37.1° C cranial temperature as measured at the tympanum (Benzinger, 1969). As cranial temperature decreases below this 'set-point', the magnitude of central inhibition of the thermogenic center is decreased and its stimulation of thermogenesis becomes dependent upon the magnitude of the peripheral cold stimulus. Present findings indicate, contrary to the suggestion of Benzinger (1969), elevations in oxygen consumption at the onset of immersion at core temperatures (tympanic, as well as esophageal and rectal sites) well above the hypothesied set point value.

That the magnitude of the peripheral stimulus is contributing to the gain of the slow component is evident from Fig. 4.16. Results of one subject only are depicted in this figure and compared with results of Benzinger (1969) and Craig and Dvorak (1966). Present results confirm and also complement the curvilinear relationship of the skin isotherms; metabolic rate plotted against tympanic temperature for three levels of skin temperature. In comparison, Craig and Dvorak observed a more linear relationship and a response of lesser magnitude.

Fig. 4.16 : Relationship between the thermogenic response and
    tympanic temperature at different levels of water
    temperature (10°, 15° and 20° C). The values of metabolic
    rate were taken after the 'fast' component of the
    thermogenic response. Data of Benzinger (1969) and of Craig
    and Dvorak (1966) are also presented for comparison.

209b
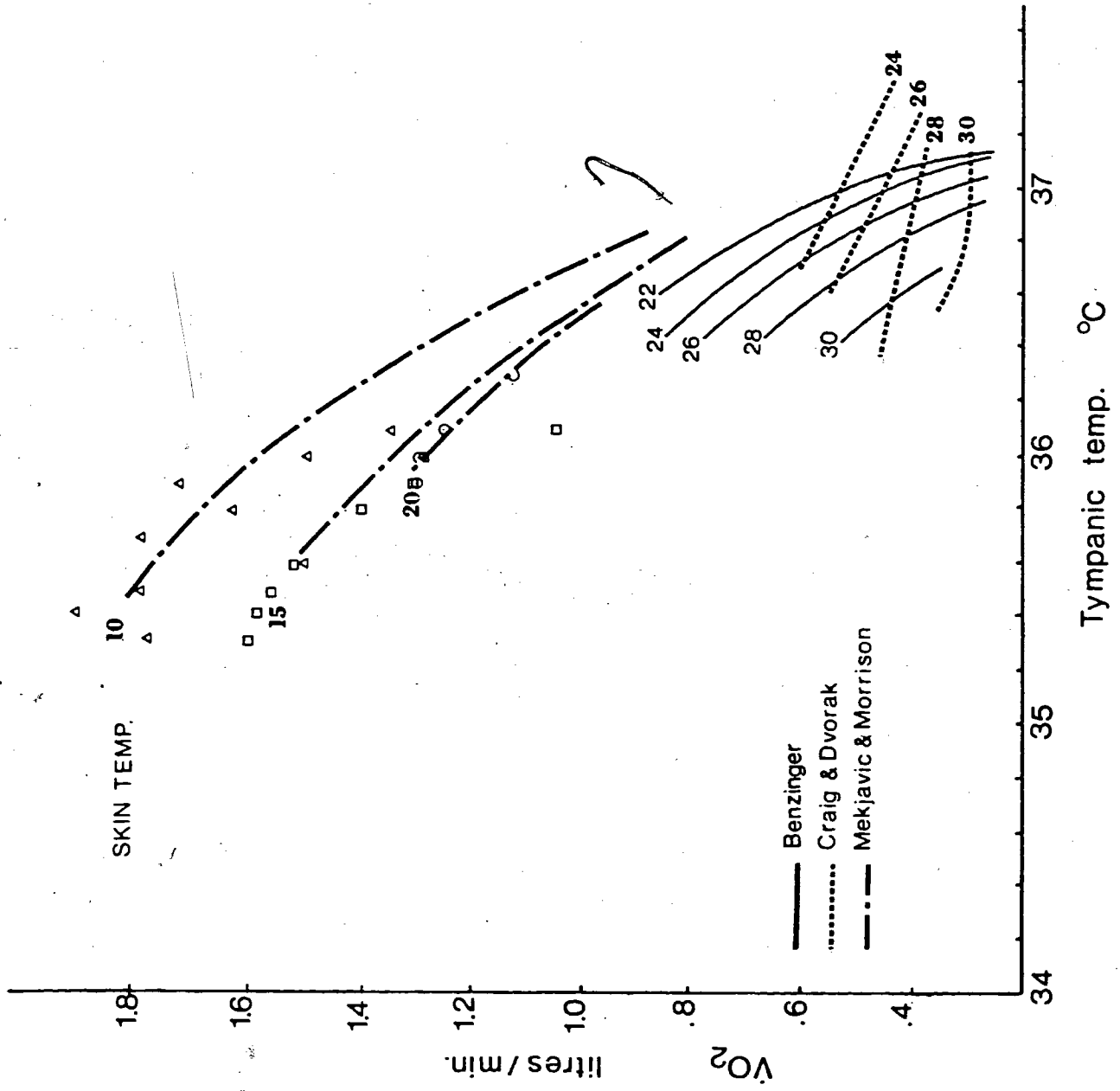
Although our results complement Benzinger's findings, they are contrary to the theoretical hypothesis explaining the relationship of the variables: namely that the skin isotherms represent the relationship between steady state skin and tympanic temperature and metabolic rate. According to Hensel (1976), the metabolic rate is proportional to the peripheral cold receptor static firing rate. The static firing characteristics of cold receptors, described by Zotterman (1953), suggests that firing rate reaches a maximum level in the temperature range of $25^{\circ} - 30^{\circ}$ C. Above and below this temperature zone, the firing rate decreases giving a bell shaped characteristic. This bellshaped curve is interrupted at approximately 12° C, where Zotterman (1953) noted a second peak in the static firing frequency of cold receptors. Whether this second pulse is the superposition of pain fiber excitation upon the cold fiber firing rate has not yet been clarified. Applying this theory to our results, the metabolic rate at a given core temperature would be expected to be lower at 15° and 10° C, than at 20° C, since the neural drive is smaller. On the contrary, our results indicate an increasing metabolic response with decreasing temperature of water, similar to Benzinger's findings. However, a dominant factor may be the rate of change of core temperature. Although it was not possible to 'clamp' core temperature, at given skin temperatures; it was possible to alter the core cooling rate at identical levels of skin temperature. As can be seen from Fig. 4.17, the metabolic

Fig. 4.17 : Relationship between the thermogenic response and
tympanic temperature at different levels of water
temperature (10°, 15° and 20° C). The values for metabolic
rate were taken after the 'fast' thermogenic component.
Closed symbols represent experiments where normal room
temperature air was inhaled, while open symbols represent
experiments where heat was donated to the thorax during
immersion in cold water (using warm saturated air as the
inhalate).

Subject B.C.

experiment:
○—○ 10 N	W ●—●	
△--△ 15 N	W ▲--▲	
□·····□ 20 N	W ■·····■	

$\dot{V}O_2$ (ml.O_2/ kg./ min.)

Tympanic temp. (°C)

211b
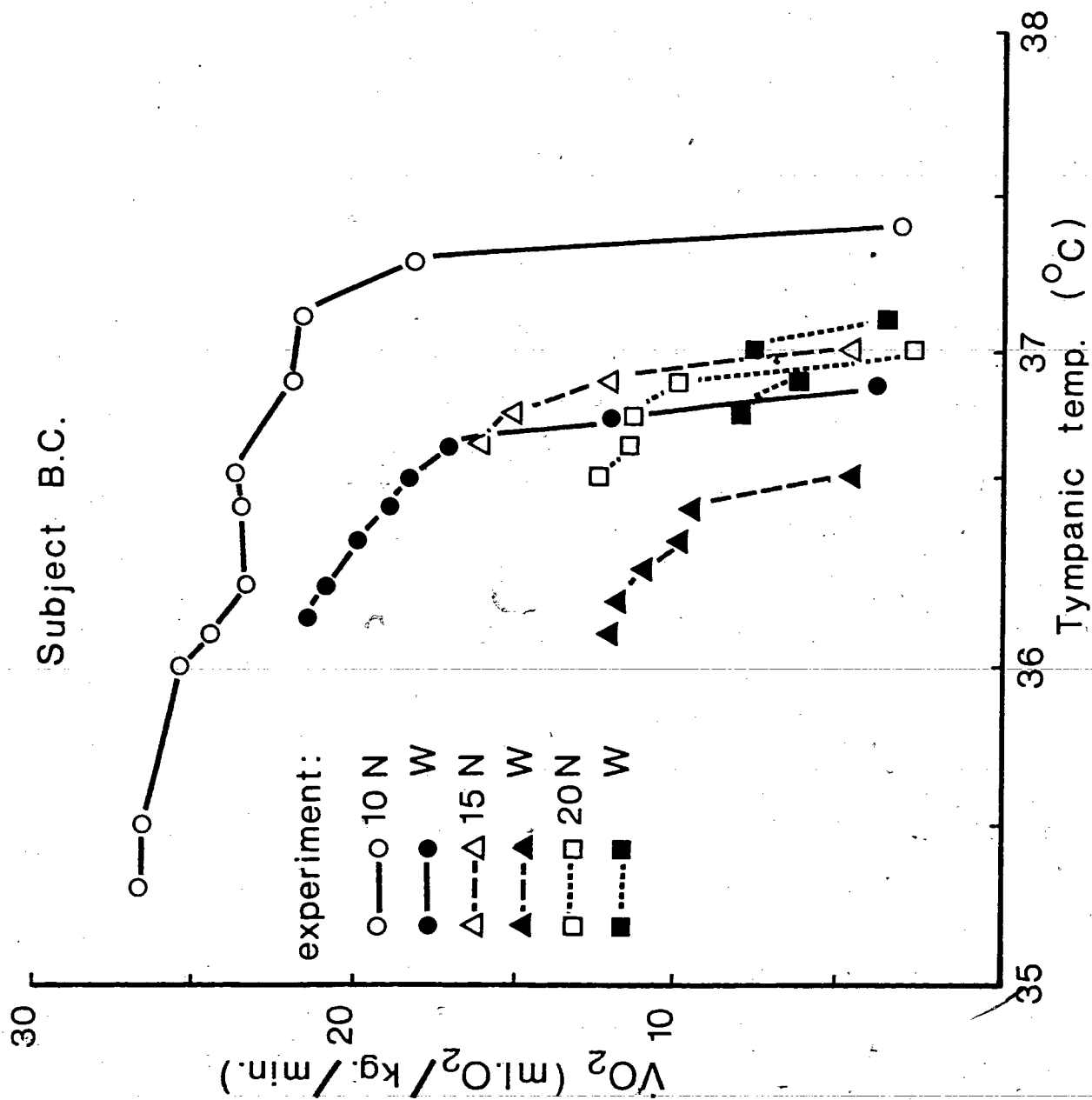
response at the same core and skin temperature, for the same subject, is lower during immersions where the inhalate was warm air saturated with water vapour. In these experiments, cooling rate of the core was lower than when room temperature air was inhaled. This implies that comparisons, such as presented in Fig.16 are meaningless, if dynamic components of core temperature are not reported. For example, comparison of experiments RH20N (Fig. 4.14) and RH20W (Fig. 4.15), at minute 15 and 30 during the immersion, respectively, indicates that skin and core (tympanic) temperature in both experiments are comparable. However, core cooling rate is much greater in experiment RH20N, which may explain the greater magnitude of shivering thermogenesis (17 ml./kg./min compared to 12 ml./kg./min of oxygen consumed). Similar differences in core cooling rate may exist between the results of Benzinger (1969) and Craig and Dvorak (1966). Assuming that core cold receptors have similar characteristics to skin cold receptors, then they should be considered as having dynamic and steady state responses. Therefore, their firing response will not only be a function of the core temperature, but also of the cooling rate of the core.

In the warm air breathing trials, the inhibition of the thermogenic centre appears to be enhanced by additional heating of the core such that it suppresses the magnitude of the metabolic overshoot. Present findings suggest therefore, that the central inhibition of thermogenesis should also be included

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as a controlling factor during the fast component stage of the thermogenic response.

Analysis of individual experiments reveals that it is difficult in human experimentation to separate effects due to peripheral stimulation from metabolic responses resulting from core cooling. It becomes apparent that thermogenesis results from an integrated core and skin stimulus, which is subsequently suppressed by cranial warm receptor activity; more specifically warm sensitive neurones in the pre-optic anterior hypothalamus. Although the existence of extra-hypoyhalamic warm receptors within the core and their contribution to the thermogenic response in humans has not been identified, they should not be completely ruled out as possible contributors to the warm inhibition of thermogenesis.

Integration of core and skin thermal stimuli could explain the intense thermogenic response observed in subject RH in all experiments. Since core cooling commences immediately on immersion, the separation of the fast component and slow phase of the metabolic response may be masked by the early onset of the slower component. At the other extreme, subject DS with a much higher endomorphic component and thus a very slow cooling rate in 15° and 20° C water, exhibits an almost negligible slow component.

In summary therefore, the thermogenic response during cold water immersion appears to be a result of an integrated stimulus of static and dynamic skin surface and body core cold receptor

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activity, inhibited by the static and dynamic hypothalamic warm receptor activity. At the onset of immersion, a fast thermogenic component appears mainly as a result of dynamic skin temperature changes. Once skin temperature stabilizes at a static level, a constant cold stimulus will be generated from the skin cold receptors. Depending on the subjects body composition, core temperature may remain at a fairly steady state level for a short period of time, before the onset of cooling. This steady state level at approximately normothermia, will offer varying degrees of suppression of thermogenesis. The subsequent slow component will arise from a combination of a growing steady state stimulus from the skin coupled with a quasi-static or dynamic stimulus from the core receptors. The extent of the dynamic component will be a function of core cooling rate.

Thus, it seems that human thermoregulatory responses may be explained with the aid of neural response characteristics of thermosensitive structures involved in thermal homeostasis. This approach may have useful applications in the field of thermoregulatory modelling. Existing neuronal models of thermogenesis only describe excitatory and inhibitory pathways within the thermoregulatory system and do not attempt to quantitatively correlate neural activity with thermogenesis. Conversely, models predicting metabolic rate during cold exposure do not account for the activity of surface and core thermosensitive neural structures; tending to treat the output drive to thermogenesis as a time independent linear function of

static core and peripheral temperatures. To date there has been no attempt to model physiological responses to cold exposure on the basis of the characteristics of neural structures involved with maintaining normothermia. It would appear, that such an approach would not only improve prediction of shivering thermogenesis, but also better represent physiological thermoregulation.

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E. A MODEL OF SHIVERING THERMOGENESIS BASED ON THE NEUROPHYSIOLOGY OF THERMORECEPTION

I. Introduction

Numerous reviews of thermoregulatory modelling (Bligh, 1973; Bligh and Moore, 1972; Hardy, 1972; Hsu, 1971; Hwang and Konz, 1977; see also section B this thesis) indicate that, in the past there have been two distinct thermodynamic approaches to the simulation of human thermal homeostasis. One approach has been to quantify the heat transfer within the human body under certain environmental conditions (Gagge, 1977; Hsu, 1971; Wissler, 1961, 1964; Wyndham and Atkins, 1960). In addition, attempts have been made to predict the rate of metabolic heat generation due to shivering in response to a cold stimulus (Brengelmann, 1967; Hayward et al., 1977; Nadel et al., 1970; Stolwijk and Hardy, 1966). More recently, complex computer models evaluating heat transfer within the human body, have incorporated the set-point theory (Hammel et al., 1963) to account for shivering thermogenesis in various regions of the human body (Montgommery, 1974 a,b ; Riggs, 1976; Stolwijk, 1970; Wissler, 1970).

The set-point theory, as initially proposed by Bazett (1949) and Vendrik (1959) and later advanced by Hammel et al. (1963), suggests that peripheral and core temperatures are compared to a central reference level. The net result of such a comparison is an error or effector signal. A combination of effector signals initiated from peripheral and central regions

of the body is proportional to the shivering thermogenesis.

It has been found in section C that models incorporating the set-point theory generate systematic errors of prediction. The results of the statistical analysis confirmed the findings of Hwang and Konz (1977), that most models incorporate theoretical coefficients of regression, which are only appropriate for the subject pool, from which the models are derived.

Although some models suggest that they are accounting for the responses of cold and warm receptors to thermal stimuli (Stolwijk, 1970; Montgommery, 1974 a,b), they only use values of temperature and hence the bell shaped characteristics of the cold and warm receptors, described by Zotterman (1953), not are incorporated in the models. An analysis of the residuals generated by models predicting shivering thermogenesis from peripheral and core temperatures, indicated that response characteristics of thermoreceptors, should be incorporated as weighting factors for skin and core temperature drives. Much insight has been gained into the static and dynamic characteristics of cold and warm receptors (Duclaux and Kenshalo,1980; Hensel and Boman, 1960; Iggo, 1969; Kenshalo and Duclaux, 1977; Zotterman, 1953). There are, however, insufficient data available on the integration of neural coded thermal signals at the spinal and hypothalamic level.

Using physiological data obtained in section D and neurophysiological evidence presented in the literature, an

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attempt has been made to develop a time dependent model of shivering thermogenesis. The neurophysiological data pertains to the response characteristics of thermosensitive neural structures. Since the response characteristics were obtained from neural structures in cats and primates, it was necessary to scale the findings to observations made in man (Hensel and Boman, 1960; Hensel, 1982). As there is a lack of knowledge on the distribution of thermoreceptors in the human body and the nature of the integration of neural coded temperature information, some assumptions have been necessary.

II. Development of Model

The thermogenic control system in man may be categorized into three main components :

- Temperature sensing component. Transduces thermal energy into neural coded information.
- Integrative component. Integrates the thermal information from various regions in the body.
- Effector component. Initiates thermogenesis in response to the neural coded thermal information.

Neural information from thermal transducers, or thermoreceptors, is integrated at various levels of the nervous system. The cumulative signal, incorporating excitation and inhibition, is proportional to an increase in heat production, for a given cold stimulus. For the purpose of clarity, following a general description of the proposed model, the solution of this network is divided into separate analysis of the three components.

General Description of Model

The model depicted in Fig. 5.1, considers shivering
thermogenesis as a net result of thermoreceptor excitation and
inhibition from various core and skin regions in the body.
Excitatory neural drive is derived from temperatures of the
skin, obtained from the arm (lateral aspect of upper arm), chest
(mid axillary, approximately at the fifth intercostal region),
thigh (anterior aspect) and calf (lateral aspect). Core cold
excitatory drive is obtained from temperatures of the rectum (15
cm. beyond anus) and in the esophagus (at the level of the
atria).

Although there is sufficient evidence supporting the theory
of peripheral cold excitation of shivering thermogenesis
(Benzinger, 1969; Craig and Dvorak, 1966; Hayward et al., 1977),
there is as yet little information on the contribution of the
various peripheral regions to thermogenesis. Intuitively it
would seem, that such a relationship would depend on the density
of the cold receptors in the skin of a peripheral region, as
well as the mode of integration of this information in
extrahypothalamic regions and hypothalamic centres. For
simplicity, the skin regions are not weighted and are considered
individually, rather than obtaining a mean skin temperature. The
neural drives determined from each skin region are summed for
the purpose of obtaining an excitatory thermogenic drive from
skin cold receptors. Due to the non-linear characteristics of

Fig. 5.1 : Concept of model.

226b
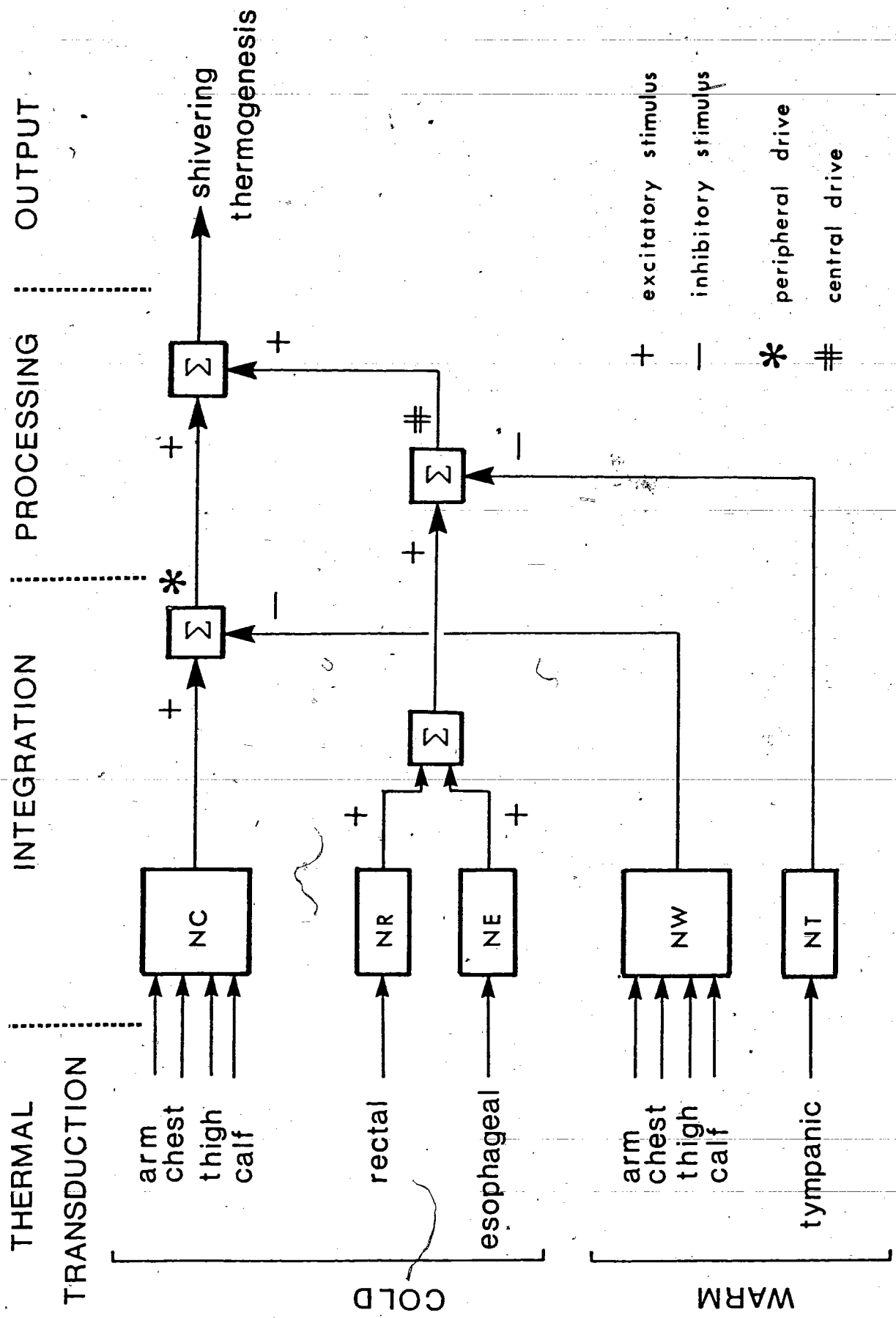
the thermoreceptors, the resultant thermogenic drive may differ substantially from that which would be computed from a mean skin temperature.
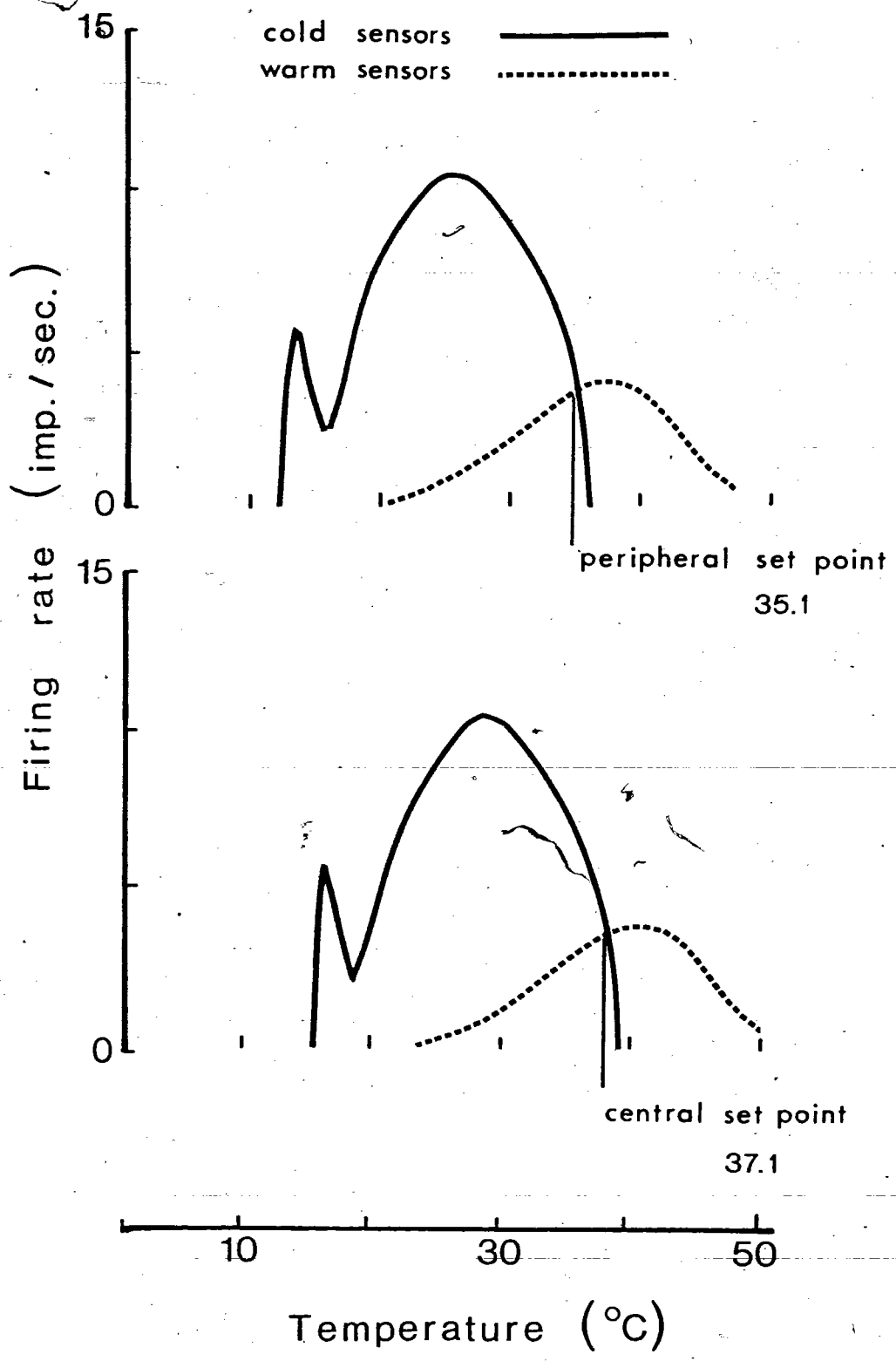
To account for the thermogenic effector mechanisms induced by core cooling, as observed in the ewe (Rawson and Quick, 1972) and in man (Piantadosi et al., 1981), a core cold excitatory drive is included in the model. Again, the distribution of thermosensitive structures in the core region of the trunk is unknown. Two core trunk sites are used, selected primarily for ease of obtaining temperature information. It is assumed that by considering esophageal and rectal temperature, some consideration is also taken for the temperature of the spinal cord, as thermal variation of the spinal cord affects the transmission and coding of neural temperature information to the hypothalamic thermoregulatory centres (Simon, 1974).

The inhibitory neural drive to the thermogenic centre is derived from neural coded thermal information generated in two regions of the body. Warm receptors in the skin region (measured at the same sites as for cold reception) are treated in the same manner as described for cold receptors. The inhibitory drive from the heat loss centre in the pre-optic anterior hypothalamus is assumed to be indicated by tympanic temperature.

A fundamental feature of the model is therefore the establishment of a core and peripheral set-point, thus enhancing the theory of central inhibition of thermogenesis (Benzinger, 1969), by suggesting there exists a certain amount of peripheral

inhibition of thermogenesis. The former is accounted for by considering tympanic temperature as an inhibitory drive and the latter by including inhibition by skin warm receptors. The model establishes a modified version of the Bazett - Vendrik (Bazett, 1949; Vendrik, 1959) set point hypothesis. This hypothesis suggests that the set-point is established by the characteristics of central cold and warm sensors. However, this theory alone is not adequate to explain the initiation of thermogenic effector mechanisms in the absence of shifts in core temperature, when only skin temperatures have been displaced (Hayward et al., 1977; Nadel et al., 1970). A peripheral set-point was incorporated, by inclusion of the characteristics of skin cold and warm receptors. Comparing static and dynamic characteristics of cutaneous thermoreceptors (Hensel, 1982) and central thermoreceptors (Poulos, 1981), it seems that the general bell-shaped response curve (Fig. 5.2) is shifted towards higher temperatures for central thermoreceptors. Considering the set-point as a temperature, where the firing rates of warm and cold receptors are identical (Vendrik, 1959), this would imply that the central set-point is higher than the peripheral, skin set-point. This difference in set-point values is taken into account by the present model, as seen in Fig. 5.2 .

Fig. 5.2 : Peripheral and central set point temperatures of present model.

cold   sensors ———
warm   sensors ·············

peripheral set point
35.1

central set point
37.1

Firing   rate   (imp./sec.)

Temperature   (°C)

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Simulation of Thermoreceptor Response

Experimentors studying isolated cold and warm receptors (Duclaux and Kenshalo, 1980; Hensel and Boman, 1960; Iggo, 1969; Kenshalo and Duclaux, 1977; Zotterman, 1953) have concluded that the response to temperature change of single thermosensitive units is a dynamic overshoot or undershoot in firing frequency, which subsides to a steady state tonic activity. Whether the dynamic phase consists of an overshoot or undershoot is determined by the direction of the temperature gradient and the type of thermoreceptor (cold or warm receptor). The latter phase of the response is often referred to as adaptation. Fig. 5.3 illustrates this concept with respect to cold and warm receptors.

The simulation of response characteristics of thermoreceptors consists of static and dynamic components. As indicated by Duclaux and Kenshalo (1980) and Kenshalo and Duclaux (1977), the dynamic response is proportional to the magnitude of the step change in temperature and the static responsiveness at the adaptive temperature.

Static Response

From the above studies, it is apparent, that there is considerable variation in the response curves of single units. In general, they are bell shaped with peaks in the range of 20°
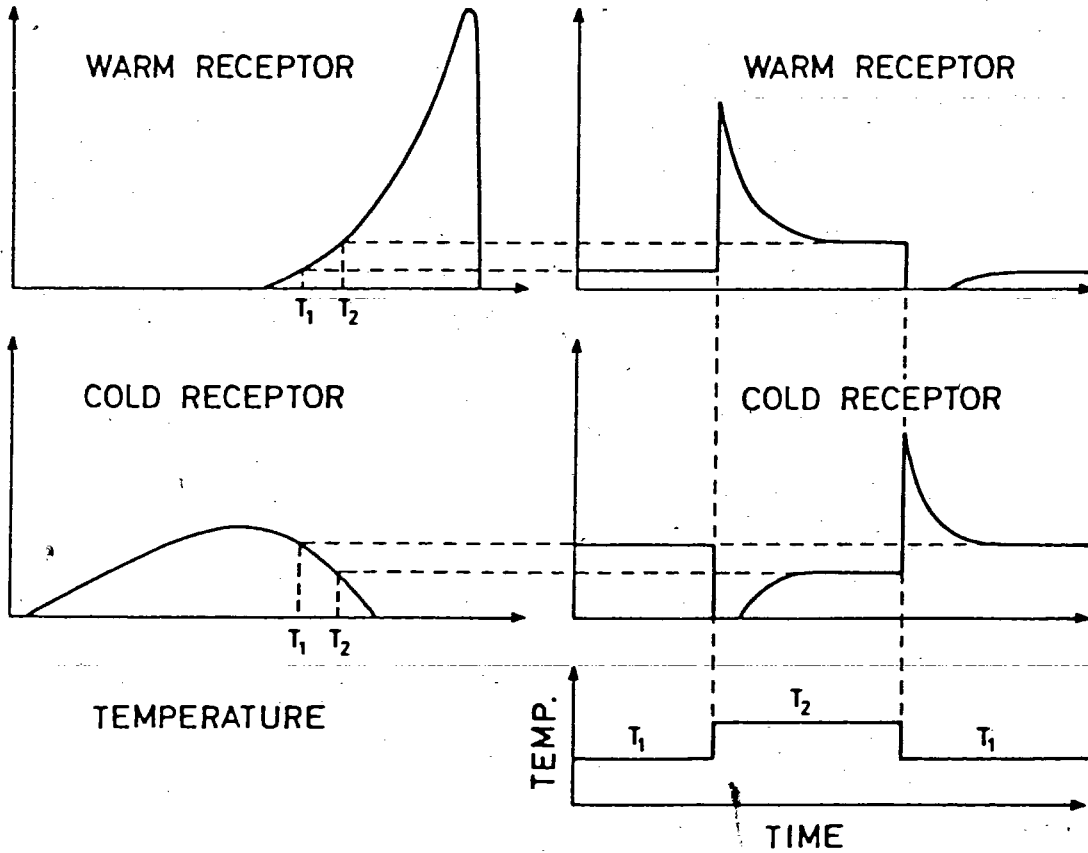
Fig. 5.3 : Static and dynamic response characteristics of cold and warm receptors.

STATIC   DYNAMIC

IMPULSE FREQUENCY

WARM RECEPTOR

WARM RECEPTOR

T_1 T_2

COLD RECEPTOR

COLD RECEPTOR

T_1 T_2

TEMPERATURE

TEMP.

T_1 T_2 T_1

TIME

231b

to 30°C for cold receptors and 40° to 45°C for warm receptors. Using the averaged response characteristics reported by Zotterman (1953), two tenth order polynomials were derived to simulate the relationship between frequency of discharge and adaptive temperature :

-static firing rate of cold receptor, Fcold :

$$Fcold(impulses/sec.) = P0 + P1*T1 + P2*T^2 + P3*T^3 + \ldots\ldots \ldots + P10*T^{10} \qquad \ldots(5.1)$$

-static firing rate of warm receptor, Fwarm :

$$Fwarm (impulses/sec.) = Q0 + Q1*T + Q2*T^2 + Q3*T^3 + \ldots\ldots \ldots + Q10*T^{10} \qquad \ldots(5.2)$$

where,

T = adaptive temperature $p(i)$, $q(i)$; i=1,10 = coefficients of regression.

The derived coefficients of regression for equations 5.1 and 5.2 are given in Table 5.1.

Table 5.1 : Coefficients of tenth order polynomials predicting
static firing rate of cold and warm receptors.

Coefficients for tenth order polynomials

in equations 5.1 and 5.2

order of polynomial	cold receptor		warm receptor	
0	-.19005313	E6	.1526647	E5
1	.85318078	E5	-.5147704	E4
2	-.16974919	E5	.7707699	E3
3	.19724509	E4	-.67475955	E2
4	-.14833377	E3	.38244284	E1
5	.75486723	E1	-.14664175	E0
6	-.26343323	E2	.38526706	E-2
7	.62289589	E-2	-.68496075	E-4
8	-.95563808	E-4	.78889647	E-6
9	.85949930	E-6	-.53173142	E-8
10	-.34432887	E-8	.15936041	E-10

	cold receptor	warm receptor
residual mean square	.02074	.00314
multiple r^2	.99834	.99874
lower temperature limit	12.6°C	23.6°C
upper temperature limit	35.4°C	45.6°C

Dynamic Response

Kenshalo et al. (1974) have suggested that the transient phase of the thermoreceptor responsiveness is a result of certain excitatory and inhibitory mechanisms. During a transient step change in temperature, the activity of each mechanism decays exponentially, such that :

-excitatory mechansim, E :

$E = \exp(-t/Ke)$ ...(5.3)

-inhibitory mechansim, I :

$I = \exp(-t/Ki)$ ...(5.4)

where,

Ke = time constant for decay of excitatory action =

= 5.5 seconds .

Ki = time constant for decay of inhibitory action =

= 3.3 seconds .

The transient component of the net change in the firing frequency of a thermoreceptor due to a step change in temperature is described in the present model as :

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$$Ftrans.(t) = P \times A \times (E(t) - I(t)) \qquad \ldots(5.5)$$

where,

A = gain

P = coefficient accounting for the direction of the step·change
in temperature and the type of thermoreceptor.

A step change in temperature from T1 to T2 will therefore initiate a transient response from the steady state firing rate at T1 (F1 in impulses/second) to the steady state firing rate at the adaptive temperature T2 (F2 in impulses/second) . The transient phase will depend on the magnitude of the step change :

$$S = F2 - F1 \qquad \ldots,(5.6)$$

as well as on the initial temperature, prior to the stimulus :

$$A = F1 \times ABS(S) \times G \qquad \ldots(5.7)$$

where,

G = Gain. It was determined that a value of 5.0 would allow for adequate scaling of thermoreceptor responsiveness to that observed in humans (Hensel, 1982).

The direction of the transient response (overshoot or undershoot) is determined by P :

$$P = D \times Z \qquad \qquad ...(5.8)$$

where,

D = 1 , for cooling (negative step change in temperature).

=-1 , for warming (positive step change in temperature).

Z = 1 , for cold receptor simulation .

=-1 , for warm receptor simulation .

In equation 5.5 therefore, a positive parameter P results in an overshoot :   positive P = cooling of cold receptor = warming of warm receptor. A negative parameter P results in an undershoot during the transient phase :   negative P = warming of cold receptor = cooling of warm receptor.

Total Thermoreceptor Response

The discharge in neural impulses from thermoreceptors, in response to a thermal stimulus, can be described as a control system under proportional derivative control. Such a system consists of a proportional or pure gain component and a differentiator, allowing for derivative control. The function of the derivative control is to affect the response times and in

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extreme cases, to cause either over- or undershooting of the transient response.

The total step response of a thermoreceptor can be described as :

$$F\ (t) = A0\ x\ (\text{step response}) + A\ x\ (\text{impulse response}) =$$
$$= A0\ x\ F(t) + A\ x\ (dF(t)/dt) \qquad \qquad ...(5.9)$$

where,

A0, A = constants .

The step response is considered as :

$$F\ \text{step}\ (t) = 1 - \exp(-t/K) \qquad \qquad ...(5.10)$$

Therefore, the total neural response, incorporating equations 5.5 and 5.10 can be defined as :

$$F\ (t) = A0\ x\ (\ 1 - \exp(\ -t/K\ ) +$$
$$+ P\ x\ A\ x\ (\ \exp(\ -t/Ke\ ) - \exp(\ -t/Ki\ )\ ) \ ...(5.11)$$

where,

A0 = gain of step response = S = F2 - F1 .

K = static gain = 5.5 seconds.

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Simulation of Total Neural Drive from a Thermoreceptive Field

Temperature data from cooling studies on humans, is usually reported in the literature at time increments of one minute. This is inadequate for simulating the dynamic neural drive from a peripheral or core region, as the transient phase is usually completed within 30 seconds (Kenshalo et al., 1974). The present model obtains 2-second data points through linear interpolation between minute values for core and skin temperatures. For each 2-second increment, a time dependent neural response , F(t), is obtained according to equation 5.11 .

The derived 2-second neural responses are added according to the theory of superposition, to obtain a total neural output, N(t), from a particular region :

$$N(t) = \sum_{i=0}^{t} F_i(t-i) \qquad \qquad ...(5.12)$$

where,

$$i \rightarrow t \qquad \qquad ...(5.13)$$

in 2- second increments.

On the basis of equations 5.12 and 5.13, the total neural drive is derived from all peripheral and core regions. Depending on the parameter P, this drive will be excitatory (arm, chest, thigh, calf, rectal and esophageal cold receptor regions) or inhibitory (arm, chest, thigh, calf and tympanic warm receptor regions).

Integration of Thermal Neural Coded Information

Although various weighting formulae exist for determining mean skin temperatures (Ramanathan, 1964), the present model derives neural output from all four regions (arm, chest, thigh and calf) independently. The total neural drive from the four regions is summated to obtain a total skin neural drive :

,- excitation :

$$NCskin(t) = (NCarm(t) + NCchest(t) +$$

$$+NCthigh(t) + NCcalf(t)) / 4 \qquad ...(5.14)$$

- inhibition :

$$NWskin(t) = (NWarm(t) + NWchest(t) +$$

$$+NWthigh(t) + NWcalf(t)) / 4 \qquad ...(5.15)$$

where,

NC = denotes neural output of cold receptor field .

NW = denotes neural output of warm receptor field .

As mentioned previously, the mode of integration of neural drives from various regions, as depicted in Fig. 5.1, is derived from information available in the literature and reviewed by Bligh (1973), Hensel (1982) and Simon (1974). However, it is not possible to assign weighting factors to the individual neural drives when attempting to determine the thermogenic response. The individual neural outputs were used to obtain a relative thermogenic drive as discussed in the following section and subsequently the weighting factors for the thermogenic drive were determined through regression analysis.

Thermogenic Output Determined from the Total Neural Drive of Individual Regions

Shivering thermogenesis is usually quantified from oxygen consumption measurements during cold exposure. As there is little information available on the kinetics of oxygen consumption during cold exposure, the response characteristics

were determined from studies on the dynamics of gas exchange during exercise (Bakker et al., 1980; Cerretelli et al., 1966; Lemon et al., 1980; Prampero et al., 1970; Sherril and Swanson, 1981; Whip and Wasserman, 1972). It is generally reported, that the time course of oxygen consumption during aerobic work of medium intensity is in the order of thirty seconds. Most studies do not report a time lag between onset of exercise and increase in oxygen consumption. From their analysis of the effects of sinusoidal and impulse type workloads on the cardiorespiratory variables, Bakker et al. (1980) determined a phase lag of 22 to 24 seconds between onset of the impulse type exercise stress and oxygen consumption. Their model has been critically evaluated by Sherril and Swanson (1981), who suggested that the predicted delay of Bakker et al. (1980) is actually -7 seconds, which has no physiological basis. For the purposes of the present model, a time delay between onset of thermal stimulus and thermogenesis, is neglected.

The general response of oxygen consumption to a thermal stress is considered as an overdamped system, whose output may be described as :

$$\Delta MR(t) = (1 - \exp(-t/30)) \qquad \qquad ...(5.16)$$

where,

$\Delta MR(t)$ = change in metabolic rate =

= change in oxygen consumption ($VO2$).

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Using the hypothetical neural output from each excitatory and inhibitory region considered, a relative (dimensionless) thermogenic drive was determined on the basis of the relationship presented in equation 5.16. It is assumed therefore, that each thermoreceptive region will generate an excitatory or inhibitory drive to thermogenesis, the magnitude being dependent on the neural response from that region. Metabolic responses are obtained for step changes in neural activity from individual regions, at 20 second intervals. The total metabolic response from a region is then considered as a superposition of all 20 second thermogenic responses :

$$Mc\,(t) = \sum_{i=0}^{t} (\,\Delta NC_i(t)\,(1-\exp(\,-(t+i)/30)\,)\,) \qquad \ldots (5.17)$$

$$Mr\,(t) = \sum_{i=0}^{t} (\,\Delta NR_i(t)\,(1-\exp(\,-(t+i)/30)\,)\,) \qquad \ldots (5.18)$$

$$Me\,(t) = \sum_{i=0}^{t} (\,\Delta NE_i(t)\,(1-\exp(\,-(t+i)/30)\,)\,) \qquad \ldots (5.19)$$

$$Mt\,(t) = \sum_{i=0}^{t} (\,\Delta NT_i(t)\,(1-\exp(\,-(t+i)/30)\,)\,) \qquad \ldots (5.20)$$

$$Mw\,(t) = \sum_{i=0}^{t} (\,\Delta NW_i(t)\,(1-\exp(\,-(t+i)/30)\,)\,) \qquad \ldots (5.21)$$

where,

i → t   in 20- second increments.

and

NC(t),NR(t),NE(t),NT(t),NW(t) = total neural drives, obtained by
superimposing the neural responses to thermal stimuli
applied at 2 second intervals to the cold receptors in the
skin (NC(t)), rectal (NR(t)), and esophageal (NE(t)) region,
as well as the warm receptors in the skin (NW(t)) and
tympanic (NT(t)) regions.

Mc(t), Mr(t), Me(t), Mt(t), Mw(t) = total hypothetical
metabolic drive, obtained by superimposing metabolic
responses to twenty second neural stimuli from the cold
receptor regions of the skin (Mc(t)), rectum (Mr(t)) and
esophagus (Me(t)), and from the warm receptor regions of
the skin (Mw(t)) and tympanum (Mt(t)).

III. Results

Gain Factors for Thermogenic Drives of Individual Regions

Two approaches were undertaken in deriving the gain factors for thermogenic drives of individual regions, in order to predict the total change in thermogenic drive from resting values, ΔMR-predicted. In the the first approach both static and dynamic responsiveness of the thermoreceptors were accounted for, while the second approach omitted dynamic properties of the thermoreceptors. To establish whether three core temperature sites are necessary for prediction of thermogenesis, three variations of the conceptual model shown in Fig. 5.1 were evaluated, using the static characteristics of the thermoreceptors only.

The first model (model A) incorporates rectal and esophageal temperatures as excitatory inputs to thermogenesis, while tympanic temperature is considered an inhibitory drive. The absolute thermogenic drive is predicted by :

Model A :

$$Mtotal(t) = p1 + p2*(Mc(t) - Mw(t) + p4*(\dot{Mc}(t) - \dot{Mw}(t))) +$$

$$+ p3*(Mr(t) + Me(t) + 2*Mt(t) +$$

$$p4*(\dot{Mr}(t) + \dot{Me}(t) - 2*\dot{Mt}(t)))$$

...(5.22)

where,

Mc(t),Mr(t),Me(t) = static excitatory thermogenic drives

instigated by neural output from cold receptors in the skin

(c), rectal (r) and esophageal (e) regions

Mw(t),Mt(t) = static inhibitory thermogenic drives instigated by

neural output from warm receptors in the skin (w) and

tympanic (t) regions.

$\dot{Mc}(t),\dot{Mw}(t),\dot{Mr}(t),\dot{Me}(t),\dot{Mt}(t)$ = dynamic components of the

thermogenic drive as instigated by dynamic responsiveness

from thermoreceptors in the various regions as defined

above.

Omitting the dynamic components of neural and thermogenic responsiveness, suggesting therefore that the gain of the dynamic components in model A, p3, is equal to zero, the above model was transformed to :

Model B :

$$Mtotal(t) = p1 + p2*(Mc(t) - Mw(t)) +$$

$$+ p3*(Mr(t) + Me(t) - 2*Mt(t)) \quad ...(5.23)$$

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In addition, an analysis was performed to evaluate whether two excitatory thermogenic drives were essential for accurate prediction of shivering thermogenesis. The models evaluated were :

Model C :

$$Mtotal(t) = p1 + p2*(Mc(t) - Mw(t)) + p3*(Mr(t) - Mt(t))$$

$$...(5.24)$$

Model D :

$$Mtotal(t) = p1 + p2*(Mc(t) - Mw(t)) + p3*(Me(t) - Mt(t))$$

$$...(5.25)$$

The gains for the individual thermogenic drives (p1, p2, p3 and p4) were determined using a regression analysis (Dixon et al. 1979). The statistical package fitted the best parameters for determining the absolute metabolic rate during cold water immersion and rewarming in units of ml.O2/kg./min., using the empirical data obtained in section D. The constant p1, in equations 5.22 to 5.25, may also be interpreted as the resting, or pre-immersion, metabolic rate obtained at the neutral 'set point' temperatures. However, this constraint was not placed on the regression analysis. The parameter p1 was allowed to assume values between 1.0 and 10.0 . The constraints placed on

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parameters p2, p3 and p4 were that these parameters should be positive. Since the dynamic responsiveness of the peripheral and core thermoreceptors were assumed to be identical, the gain of the peripheral and core dynamic components were considered to be identical (p4).

Each model (A, B, C and D) was developed with the cooling and rewarming data obtained from a total of thirty cold water immersion and rewarming trials. Five subjects underwent immersions in three different water temperatures (10°, 15° and 20° C) twice. On one occasion the inhalate was room temperature air, while on the second occasion the inhalate was warm saturated air (40° - 45° C, saturated with water vapour). In this manner, for three levels of clamped skin temperature, two core temperature cooling rates were induced for each subject. Similarly, several rewarming rates were obtained for each subject.

The regression analysis was conducted on the results of each subject individually, thereby obtaining personalized gain parameters p1, p2, p3 and p4. The personalized gain parameters obtained for each model on individual subjects are presented in Table 5.2 . The error, as indicated by the sum of the squared residual (SSR), generated by the models for different subjects varies considerably. This is partly due to the different number of sample observations. Comparing the errors generated by the different models for individual subjects (Table 5.2), it is apparent that the differences in the sum of the squared

Table 5.2 : Comparison of sum of the squared residual (SSR)
generated by four models (A, B, C and D) on five subjects.
Personalized coefficients were derived for individual
subjects.

Subj.	Model	SSR	MSE	P1	P2	P3	P4
AL	A	8240.64	18.44	7.06	.422	.582	.531
	B	8466.38	18.9	7.96	.721	.348	N/A
	C	8539.56	19.06	7.93	.653	.621	N/A
	D	8412.47	18.78	8.09	.747	.729	N/A
BC	A	14317.1	32.1	8.64	1.46	1.095	.00001
	B	14316.6	32.1	8.64	1.47	1.095	N/A
	C	16098.4	36.1	7.43	1.845	2.8	N/A
	D	14592.7	32.7	10.09	.644	1.355	N/A
DS	A	3972.82	9.35	6.6	.358	.377	.595
	B	4094.59	9.61	6.86	.435	.175	N/A
	C	4110.88	9.65	6.97	.366	.278	N/A
	D	4085.09	9.59	6.88	.455	.38	N/A
DT	A	9581.33	21.88	7.71	1.306	1.295	.00001
	B	9581.1	21.87	7.71	1.306	1.295	N/A
	C	8295.09	20.38	4.76	2.27	3.46	N/A
	D	10777.1	24.61	10.48	.235	1.58	N/A
RH	A	7996.06	22.4	10.0	1.143	.569	.00001
	B	7995.18	22.5	10.1	1.12	.562	N/A
	C	8257.27	23.19	10.23	.989	1.11	N/A
	D	8041.32	22.59	10.31	1.11	1.023	N/A

Total	A	44107.95
	B	44527.03
	C	45931.2
	D	45908.68

Note: Models D, E and F omit the contributions of the dynamic
components from core and peripheral thermosensitive regions.
The gain of the dynamic component, P4, is therefore equated
to zero.

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residuals are not significant. This is also shown with the comparison of the total sum of the squared residuals generated by the models on all five subjects (Table 5.2). Overall, there is a similarity in the gains assigned to the peripheral (p2) and core (p3) thermogenic drives. With the exception of subjects DS and AL for model A, the gain on the dynamic component (p4) is assigned low weighting values. The values of 0.00001 for p4, observed in Table 5.2, coincide with the minimum value restriction placed on p4 in the regression analysis.

Omitting the dynamic term in model A did not increase the sum of the squared residuals significantly, as observed from the results of model B in Table 5.2. The overall SSR increased from 44107.95 for model A to 45858.02 for model B. It is also evident from Table 5.2, that using either only the rectal (model C) or only esophageal (model D) static excitatory thermogenic drives, results in similar magnitudes of errors.

A best fit regression analysis was conducted on the combined data of the five subjects. The analysis revealed, that the following equations were best predictors of shivering thermogenesis in the present subjects :

Model A :

$$Mtotal(t) = 8.01 + 0.592*(Mc(t) - Mw(t) +$$
$$+ 0.28*(\dot{Mc}(t) - \dot{Mw}(t))$$
$$+ 0.771*(Mr(t) + Me(t) - 2*Mt(t) +$$
$$+ 0.28*(\dot{Mr}(t) + \dot{Me}(t) - 2*\dot{Mt}(t))) \qquad ...(5.26)$$

Model B :

$$Mtotal(t) = 8.18 + 0.901*(\ Mc(t) - Mw(t)\ ) +$$
$$+ 0.678*(\ Mr(t) + Me(t) - 2*Mt(t)\ )$$

$$...(5.27)$$

Model C:

$$Mtotal(t) = 8.45 + 0.675*(\ Mc(t) - Mw(t)) +$$
$$+ 1.16*(\ Mr(t) - Mt(t)\ ) \qquad ...(5.28)$$

Model D :

$$Mtotal(t) = 8.73 + 0.771*(\ Mc(t) - Mw(t)\ ) +$$
$$+ 1.199*(\ Me(t) - Mt(t)\ ) \qquad ...(5.29)$$

where,

$Mtotal(t)$ = predicted metabolic rate in units of ml.O2/kg./min.
at time t.

On the combined data, the gain on the core thermogenic drive is given more weighting, when compared to the peripheral gain.

Comparative Evaluation

An evaluation was conducted on the models A, B, C and D, by comparing their power of prediction with that of the models suggested by Hayward et al. (1977),model H, and Nadel et al. (1970), model N. Of the models evaluated in section C, the models of Hayward et al. (1977) and Nadel et al. (1970) proved to have the best overall capability of predicting shivering thermogenesis. Both models are based on the set-point concept and define peripheral and core set-point temperatures. However, no allowance is made for central or peripheral inhibition from warm sensitive receptors. The model of Hayward et al. (1977) predicts the absolute metabolic rate, while the expression of Nadel et al. (1970) predicts the increase in thermogenesis from resting values, as shown in equations 5.30 and 5.31 :

Hayward et al. (1977) :

$$MR \ (W./kg.) = 0.0356*(Ts-41.8)*(Tt-41.0) \qquad ...(5.30)$$

Nadel et al. (1970) :

$$\Delta MR \ (kcal./hr.) = 36*(36.5-Tt)*(32.2-Ts)+$$
$$+7*(32.2-Ts) \qquad ...(5.31)$$

As observed in equation 5.31, Nadel et al. (1970) include

an additional term for skin temperature in their predictive

expression, to account for increases in thermogenesis due to

displacement of peripheral temperature in the absence of core

temperature changes.

Using the same subject data, a best fit to the formulae in

equations 5.30 and 5.31 was established using a regression

analysis. To minimize the error as much as possible, the

set-point values, as well as the gains were assumed to be

unknown. The restriction on p1 in Table 5.3 was, that it must

assume a value in the range 1.0 to 10.0 . The parameter p1 was

included in the model of Nadel et al. (1970), so that absolute

metabolic rate could be determined . This parameter is therefore

a function of resting metabolic rate and the restrictions placed

on it are identical to the restrictions placed on p1 in model A,

B, C and D. From Table 5.3 it is evident that in model N, the

set-point for the skin temperature, p4, assumes physiologically

reasonable values, with minimum variability between subjects. In

contrast the tympanic set-point for model N, p3, varies

considerably between subjects and in all but one subject (BC),

assumes values which cannot be justified physiologically.

Similar variations in set-point temperature values are observed

with the model of Hayward et al. (1977), however the magnitude

of the variation of the tympanic set-point, p3, is not as large

(Table 5.3). In addition, the magnitude of the variations of the

gains p2 and p5 for model N and p1 for model H does not appear

Table 5.3 : Residual analysis of models suggested by Hayward et al. (1977), model H, and Nadel et al. (1970), model N. Personalized set points and gains were determined for five subjects.

Model H – Hayward et al. (1977) :

MR = P1 (P2 − Ts) (P3 − Tt)

Subj.	SSR	N	MSE	P1	P2	P3
AL	8297.6	451	18.52	.0129	128.45	41.78
BC	17512.0	449	39.26	.2043	42.04	39.43
DS	4121.8	429	9.68	.00096	111.8	125.38
DT	13704.3	441	31.29	.00098	45.24	98.92
RH	7760.3	359	21.8	.0091	52.19	88.54

Model N – Nadel et al. (1970) :

MR = P1 + P2 (P3 − Tt) (P4 − Ts) + P5 (P4 − Ts)

Subj.	SSR	N	MSE	P1	P2	P3	P4	P5
AL	8252.8	451	18.5	8.22	.107	.0001	34.46	3.84
BC	17524.3	449	39.47	1.0	.218	39.22	40.63	.00011
DS	4117.5	429	9.69	6.57	.0014	79.3	36.35	.018
DT	13621.0	441	31.24	10.0	.0001	.0246	28.67	.592
RH	6608.6	359	18.56	10.0	.372	.0008	30.01	13.97

Note:

MR – denotes predicted metabolic rate in units of ml.O_2/kg./min.

Tt – tympanic temperature

Ts – weighted mean skin temperature form four sites (see Ramanathan, 1964)

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acceptable in terms of modelling the thermogenic response for a large population of individuals.

Since the set-points for peripheral and core thermogenic drives are constant in models A, B, C and D and only gains were determined by regression analysis, it seemed appropriate to conduct a comparison of the models derived in this thesis with the models of Hayward et al. (1977), model HS, and Nadel et al. (1977),model NS, using the set-points suggested by the authors and allowing only the gains to be determined by the regression analysis. This comparison was conducted with the combined data of all five subjects (N=2129) and the results are tabulated in Table 5.4 . In these comparisons, model D, utilizing static excitatory thermogenic drive from only the esophageal region, generated the least amount of error as indicated by the SSR. The sum of the squared residuals are not significantly different from those generated by model A, incorporating rectal and esophageal thermogenic drives with both static and dynamic characteristics. In comparison with the expressions suggested by Hayward et al. (1977) and Nadel et al. (1970), model D proved to be significantly better in predicting the overall thermogenic response of the five subjects.

When conducting these comparisons, it is essential to also observe the number of parameters and independent variables utilized by the models. The number of independent variables implies the number of variables that are independent of one another. Since c and w are derived from skin temperature, they

Table 5.4 : Comparison of four models (A, B, C and D) developed in this thesis, with those of Hayward et al. (1977) and Nadel et al. (1970). The residual analysis was conducted on the combined data of five subjects. The table also reveals the error generated (sum of the squared residual, SSR) by models H and N, if the set points are constrained to values suggested by the authors, as in models HS and NS.

MODEL	SSR	MSE	P1	P2	P3	P4	P5
A	65542.1	30.84	8.01	.592	.771	.28	N/A
B	66242.8	31.16	8.18	.901	.678	----- N/A -----	
C	70618.9	33.22	8.45	.657	1.16	----- N/A -----	
D	64679.4	30.42	8.73	.771	1.199	----- N/A -----	
H	75619.8	35.57	.0078	59.46	74.67	----- N/A -----	
N	75623.1	35.6	1.0	.0086	.00033	56.18	.611
HS	92608.2	43.52	.0975	--------- N/A --------------------------			
NS	75814.4	35.6	8.312	.0228	.287	----- N/A -----	

Note:

A, B, C and D - denote models developed in present study (see text for description).

H and N   - relationships suggested by Hayward et al. (1977) and Nadel et al. (1970), respectively. No restrictions placed on gain and set point values.

HS and NS   - models H and N, respectively, but with restrictions placed on set point temperatures. Set point values considered constant and have values as suggested by Hayward et al. (1977) and Nadel et al. (1970), respectively.

constitute only one independent variable. From Table 5.4 it is evident, that model D has the same number of independent variables as models N and H, and also the same number of parameters as model H but less than model N, yet it is the best overall predictor of thermogenesis during cooling and rewarming. In the last analysis on models NS and HS, the number of parameters are reduced to 3 and 1 respectively, as the set-points are maintained at constant values.

IV. Discussion

The models used in the comparative evaluation of the present study (Hayward et al., 1977; Nadel et al., 1970) suggest that, for a variety of individuals the thermogenic response is a function of the displacement of peripheral and core temperatures from pre-determined set-point values. It has been shown, that the gains of these models show significant subject variability and are therefore not accurate in their prediction of thermogenesis for individual subjects. The analysis in section C has indicated that the errors generated by N and H do not follow a random distribution, but suggest that a functional relationship has been omitted from the models. Hensel (1976) has shown that metabolic rate is proportional to the static responsiveness of cutaneous cold receptors at a constant core temperature. The characteristics of thermosensitive neural structures have to date been omitted from thermoregulatory predictive models.

The models derived in the present study are based solely on the static and dynamic properties of cutaneous and core thermoreceptive units. Central and peripheral set-points are established on the basis of the firing frequency of cold and warm receptors. The region of thermoneutrality, where the firing frequency of these receptors is identical, is assumed to be the physiological set-point. Poulos and Molt (1976) indicated that

the static response curves of central warm and cold sensitive units assume similar shapes as cutaneous thermoreceptors, but the general bell-shaped curves (Duclaux and Kenshalo, 1980; Kenshalo and Duclaux, 1977; Zotterman, 1953) are shifted towards higher temperatures. In the present derivation, this is assumed to indicate higher core set-point temperatures, namely 37.1° for core and 35.1° C for the periphery.

The present modelling approach suggests that displacement of peripheral and core temperatures does not instigate linear changes in the thermogenic drive from core and peripheral regions respectively, but that the thermogenic drives are proportional to the static and dynamic properties of thermosensitive neural structures. In addition, the thermogenic drive is a net sum of excitatory and inhibitory output from cold and warm receptors.

In comparison with the predictive expressions of Hayward et al. (1977) and Nadel et al. (1970), the models derived in the present study were found to generate significantly less errors, as indicated by the analysis of the sum of the squared residuals. In addition to the overall improvement in prediction of shivering thermogenesis, the benefits of the present conceptual model become apparent in the results of the regression analyses of all the models on individual subjects (Table 5.2 and Table 5.3). The variation of the peripheral and core gains in all the subjects is minimal and there is a tendency to balance the two gains. In contrast there is no trend

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apparent in the gains determined by the regression analysis for models N and H. It would appear therefore, that such subject variability would account for large errors of prediction, if the gains assume constant values. This becomes apparent when fitting the models to the combined data of all the subjects. In contrast, the gains derived on the basis of the combined data for models A, B, C and D assume similar values as for individual subjects, with a slightly higher weighting given to core thermogenic drives (p3), when compared to the peripheral drive (p2).

Assumptions have been made in the derivation of the models, which may be the source of some of the inadequacies in the prediction of thermogenesis :

1. The static response characteristics of individual thermoreceptors vary, such that the characteristic bell shaped response curves are shifted to higher or lower temperatures, with varying degrees of magnitude of the peak. In the present model an averaged static response was utilized.

2. The dynamic and static characteristic of the thermoreceptors were modelled with data obtained on cats (Duclaux and Kenshalo, 1980; Kenshalo and Duclaux, 1977) and scaled to responses observed in humans (Hensel and Boman, 1960; Hensel, 1982). This was necessary as the responsiveness of human cutaneous receptors has not been investigated at low

temperatures (below 15°C).

3. The density of thermosensitive neural structures in various core and peripheral regions of the human body have not yet been defined. The contribution of a thermosensitive region to the thermogenic response may be proportional to the density and absolute number of thermosensitive structures within that region. The present conceptual models assume equal density and allow the regression analysis to assign weighting values only to the integrated core and peripheral thermogenic drives.

4. The interaction of neural coded temperature information within the spinal cord and hypothalamus are not yet completely identified in humans. Present models are based on observations made on cats (Poulos and Molt, 1976; Simon, 1974) and sheep (Rawson and Quick, 1971, 1972).

5. The peripheral and core set-point temperatures are established on the basis of averaged neural data of one region in cats. Although core set-point temperature is set at a level coinciding with thermoneutrality, the peripheral set-point temperature may be subject to variation, both from one region to another and between individual subjects. This implies that, the core thermoneutral zone is confined within much narrower limits than the peripheral thermoneutral zone.

6. The constant pl in models A,B, C and D is proportional to resting metabolic rate. In the derivation of the present models this parameter was constrained within a range wider

than the expected variation of resting metabolic rate (1.0 - 10.0 ml.O2/kg./min.) It would appear that this parameter should assume the value of the resting metabolic rate. Such a restriction would require the re-evaluation of the gain factors, as well as possible re-adjustments of the peripheral set point value.

7. The present models do not include any substantial delay functions for the thermogenic response. The time constant of the transient component of core and peripheral receptors may be longer than is assumed in the present modelling attempt. Kenshalo and Duclaux (1977) and Duclaux and Kenshalo (1980) have suggested that the transient component may consist of several exponential functions, each having a longer time constant. Since the models are based on neural mechanisms, the delays incorporated are extremely short in duration and would have a negligible effect on the response time when predicting thermogenesis. A lag in response may be introduced by hormonal mechanisms. The sudden onset of cold stress undoubtedly initiates a substantial sympathetic drive and hence a release of epinephrine. This would contribute to the overall oxygen consumption, but the contribution of this response would have a time delay.

8. The contribution of pain receptors during cold water immersion is omitted from present models, mainly due to lack of observations available of the contribution of these receptors to the thermoregulatory control mechanism.

9. The models do not account for adaptation, either at the
    receptor level or in the overall acclimatization of an
    individual. At the receptor level, this adaptation would
    represent the fatiguing of the transducing mechanism,
    resulting in decreased neural drive. From the work of Bruck
    and Hinckel (1982), it has become apparent that there may
    exist short-term central cold adaptive modifications to the
    firing characteristics of cold sensitive neurons in the
    lower brain stem. Acclimatization of individuals should
    reflect short-term adaptation as well as long term or
    genetic factors.

The models in the present study appear to predict the
thermogenic response during cold water immersion and rewarming
better than the models of Hayward et al. (1977) and Nadel et al.
(1970). As an example, in Fig. 5.4 the observed values of oxygen
consumption during immersion in $10^{o}C$ water for one subject are
compared to the values predicted by model D and models HS and NS
(Table 5.4). The response observed for model D is indicative of
models A, B and C. It is evident, that the model simulates the
thermogenic transient observed during the initial ten minutes of
immersion and the subsequent progressive elevation in metabolic
rate during the remaining period of immersion. In contrast, the
metabolic overshoot at the onset of immersion is not apparent in
the predictions of models HS and NS. In addition, these latter

Fig. 5.4 : Comparison of observed values of oxygen consumption for one subject during immersion in 10"C water and rewarming, with values predicted by models D, HS (Hayward et al., 1977) and NS (Nadel et al., 1970).

263a
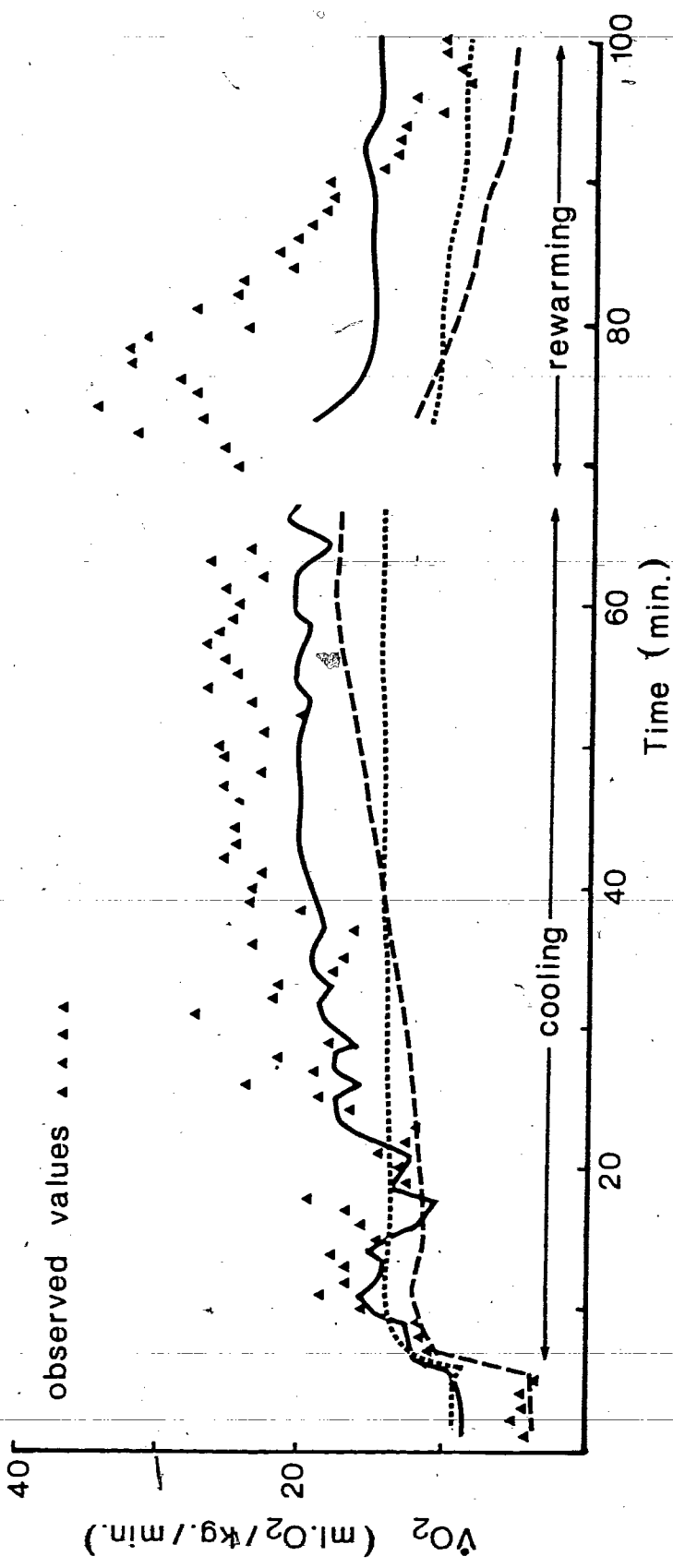
models underestimate the thermogenic response over the duration of the cold water immersion. As seen from Fig. 5.4, all the models (D, HS and NS) are inadequate in simulating the metabolic transient observed at the onset of rewarming. Model D does predict an elevated metabolic response at the start of rewarming, but is inadequate in simulating the duration of the metabolic overshoot. Models HS and NS predict a decrease in thermogenesis at the start of rewarming, resulting in greater errors of prediction.

Some of these inadequacies may arise from assumptions outlined previously. Model D in Fig. 5.4 derives its core cold excitatory drive from the esophageal region only. During the rewarming period for this subject, esophageal temperature did not exhibit an afterdrop and thus did not increase its stimulus to thermogenesis. Only the rectal temperature exhibited an afterdrop. This would suggest that, due to the different temperature responses within the core region, models C and D, utilizing only one core region for excitatory cold stimuli, may be inadequate.

Despite the shortcomings listed above, the models developed appear to have better predictive abilities than the models of Hayward et al. (1977) and Nadel et al. (1970). Although the latter models are adequate, if the characteristics of the errors are taken into account, the effects of these errors become obscured when these models are used within more complex thermoregulatory models. The model developed by Wissler (1970)

calculates the the metabolic heat production according to the model of Hayward et al. (1977). The value for the heat production is subsequently used to determine heat dissipation from various regions of the body and eventually the overall heat loss. The prediction of heat production will therefore have significant implications to the overall analysis of the model. Similarly, the complex thermal models developed by Stolwijk (1970) and Montgommery (1974 a,b) base their metabolic heat production calculations on the model of Stolwijk and Hardy (1966), which is the predecessor of the model suggested by Nadel et al. (1970) . The model of Stolwijk (1970) implies that neural drives are taken into account. These drives are equated to the skin temperature, therefore neglecting the static and dynamic characteristics of the thermosensitive neural structures.

The present study does not necessarily promote the exclusion of control systems principles in thermoregulatory modelling, on the contrary it suggests that with current knowledge of neurological mechanisms of thermoregulation, existing models should be enhanced to include this knowledge. The subsequent benefits would be apparent in the accuracy of the predictions of shivering thermogenesis.

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APPENDIX I. : Calculations and Conversion Factors

1. Determination of S.T.P.D. factor.

According to the laws of Boyle, Charles and Guy-Lussac :

$$\frac{P \, V}{T} = \text{constant for a fixed mass of gas.}$$

where, P = pressure

V = volume

T = temperature

$\frac{P \, V}{T}$ for a gas at standard temperature and pressure, dry =

$= \frac{P \, V}{T}$ for the same gas at ambient temperature and pressure saturated. In this case, P represents the sum of the dry gas partial pressures (or ambient pressure minus the vapour pressure).

or,

$$\frac{P \, V}{T}_{\text{S.T.P.D.}} = \frac{P \, V}{T}_{\text{A.T.P.S.}}$$

$$V_{\text{S.T.P.D.}} = V_{\text{A.T.P.S.}} \, (\text{S.T.P.D. factor}) =$$

$$= V_{\text{A.T.P.S.}} \, \frac{P_{\text{ambient}} - P_{\text{H2O}}}{P_{\text{standard}}} \times \frac{T_{\text{standard}}}{T_{\text{ambient}}}$$

and,

$$\dot{V}O_2 \text{ (inspired)} = \dot{V}_I \ F_{IO_2}$$

$$\dot{V}O_2 \text{ (expired)} = \dot{V}_E \cdot F_{EO_2}$$

where, F_{IO_2} = dry gas fraction of oxygen in inspired gas.

F_{EO_2} = dry gas fraction of oxygen in expired gas.

$\dot{V}O_2$ = volume of oxygen either inspired ($\dot{V}O_2 I$) or expired ($\dot{V}O_2 E$), measured in liters per minute, S.T.P.D.

$$\dot{V}O_2 \text{ (consumed)} = \dot{V}O_2 I - \dot{V}O_2 E =$$

$$= \dot{V}_I \ F_{IO_2} - \dot{V}_E \ F_{EO_2} \quad \ldots (A1.3)$$

Equation Al.1 may be rewritten as :

$$\dot{V}_E = \dot{V}_I \ \frac{F_{IN_2}}{F_{EN_2}} \quad \ldots (A1.4)$$

Substituting Al.4 in equation Al.3 :

$$\dot{V}O_2 \text{ (consumed)} = \dot{V}_I \ F_{IO_2} - \dot{V}_I \ \frac{F_{IN_2}}{F_{EN_2}} \ F_{EO_2} =$$

$$= \dot{V}_I \ (F_{IO_2} - \frac{F_{IN_2}}{F_{EN_2}} \ F_{EO_2}) \quad \ldots (A1.5)$$

where, $\dot{V}O_2$ (consumed) = volume of oxygen consumed per minute in units of liters S.T.P.D. per minute.

where, $P_{standard}$ = 760 mmHg .

$P_{ambient}$ = barometric pressure, P_B .

$T_{standard}$ = 273° Kelvin .

$T_{ambient}$ = ambient temperature, T_a (°C).

P_{H_2O} = vapour pressure, Vp.

$$V_{S.T.P.D.} = V_{A.T.P.S} \; \frac{P_B - Vp}{760} \; x \; \frac{273}{273 + T_a}$$

2. Calculation of metabolic rate .

As no nitrogen is consumed in the metabolic process, it may be assumed that the net transport of nitrogen (N_2) across the respiratory membrane is zero. Hence,

$$\dot{V} \; (inspired) \; F_{IN_2} = \dot{V} \; (expired) \; F_{EN_2}$$

assuming inspired and expired volumes of gas are corrected to standard temperature and pressure, dry. Temperature and pressure are therefore constant.

where, $\dot{V}$ (inspired) = inspired volume of air measured in liters per minute, S.T.P.D. = $\dot{V}_I$.

$\dot{V}$ (expired) = expired volume of air measured in liters per minute, S.T.P.D. = $\dot{V}_E$.

F_{IN_2} = dry gas fraction of nitrogen in inspired gas.

F_{EN_2} = dry gas fraction of nitrogen in expired gas.

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$$F_{EN_2} = 1 - F_{EO_2} - F_{ECO_2}$$

$$F_{IN_2} = 1 - F_{IO_2} - F_{ICO_2}$$

where, F_{ECO_2} = dry gas fraction oc carbon dioxide in expired gas.

F_{ICO_2} = dry gas fraction of carbon dioxide in inspired gas.

3. <u>Determination of $\dot{V}O_2$ without knowledge of the fraction of carbon dioxide in expired air (assuming a respiratory quotient of 0.85).</u>

$$\dot{V}O_2 = \dot{V}_I \quad (F_{IO_2} - F_{EO_2} \; \frac{F_{IN_2}}{F_{EN_2}})$$

and similarly

$$\dot{V}CO_2 = \dot{V}_I \quad (F_{ECO_2} \; \frac{F_{IN_2}}{F_{EN_2}} - F_{ICO_2}) \qquad \ldots (A1.6)$$

where, $\dot{V}CO_2$ = production of carbon dioxide in liters S.T.P.D. per minute.

$$R = \frac{\dot{V}CO_2}{\dot{V}O_2} \qquad \ldots (A1.7)$$

Assuming R= 0.85, then :

$$\dot{V}CO_2 = R \; \dot{V}O_2 = 0.85 \; \dot{V}O_2$$

From equations A1.5 and A1.6, it follows that :

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$$\left(F_{IO_2} - F_{EO_2} \frac{F_{IN_2}}{F_{EN_2}} \right) = \frac{1}{R} \left(F_{ECO_2} \frac{F_{IN_2}}{F_{EN_2}} - F_{ICO_2} \right)$$

$$\ldots (A1.8)$$

Equation A1.8 may be rewritten as :

$$\frac{1}{F_{EN_2}} \left(\frac{F_{ECO_2}}{R} + F_{EO_2} \right) = \frac{1}{F_{IN_2}} \left(\frac{F_{ICO_2}}{R} + F_{IO_2} \right)$$

Substituting

$$F_{ECO_2} = 1 - F_{EN_2} - F_{EO_2} \qquad \ldots (A1.9)$$

in equation A1.8 , it follows that :

$$F_{EN_2} = \frac{1 - F_{EO_2} (1 - R)}{1 + \dfrac{F_{ICO_2} + R \ F_{IO_2}}{F_{IN_2}}} \qquad \ldots (A1.10)$$

Substituting R = 0.85 in equation A1.10 :

$$F_{EN_2} = \frac{1 - F_{EO_2} (0.15)}{1.2255} \qquad \ldots (A1.11)$$

To obtain a value for oxygen consumption, equation A1.11 may be substituted in equation A1.8.

4. <u>Units for metabolic rate ($\dot{V}O_2$)</u>.

Oxygen consumption ($\dot{V}O_2$) is usually expressed in terms of liters/minute; or (when corrected for body mass) in terms of ml. O_2 /kg./min.

```
1 liter of O₂   = 4.8 kcal.
1 liter O₂/min. = 4.8 kcal./min.
1 kcal./hour    = 1.1622 Watts
1 kcal./min.    = 69.77 Watts
1 liter O₂/min. = 348.85 Watts
```

Note:

      1 Watt = 1 Joule/second = 60 J./min. =

            = .01432 kcal./min. = .8592 kcal./hour

APPENDIX II. : Construction and Position Verification of a

Thermocouple Esophageal Probe

I. Introduction

Accurate assessment of body temperature is imperative in research pertaining to thermoregulatory physiology. In order to differentiate between the thermogenetic interior and the heat exchanging periphery, the concept of a 'core and shell' has been developed by Burton (1935) and Aschoff and Wever (1958). The principle of separating the human body into two major thermodynamic components maintains, that the core consists of the cardiovascular system, the central nervous system, some components of the musculo-skeletal system and viscera, while the shell comprises of the skin, adipose tissue and the remaining muscle.

The common sites for measuring core temperatures are in the rectum, esophagus or at the tympanum. The measurements are often reported in the literature as core temperature, but are not interchangeable. Ideally, the temperature of the core should be taken at the same anatomical location for all studies and slight variations in probe placement should not cause any significant variations in the temperature measurements.

There is no adequate definition available for rectal temperature, but its value should be similar to the temperature of the blood in the visceral or trunk region. Although it may seem that rectal and esophageal temperature should be closely related, it has generally been acknowledged that rectal temperature is more 'sluggish' (Molnar and Read, 1974) or slow

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responding, while esophageal temperature is more sensitive to change.

Although rectal temperature is insensitive to peripheral stimuli, it varies considerably with depth of insertion beyond the anus. Behnke and Yaglou (1951) have shown that variations of up to 4 cm. in depth of insertion can cause a temperature difference of one degree centigrade. This difference seems to remain constant during the cooling phase (Mead and Bonmarito, 1949).

In a series of cold water immersion and rewarming trials, Hayward (1982) found that the best correlates of pulmonary blood temperature were esophageal and tympanic temperatures. These sites offered much better indication than oral, gastric or rectal temperature under the experimental conditions of cooling and rewarming. McCaffrey et al. (1975) have shown that the tympanic temperature is influenced by head skin temperature and is therefore not a good indicator of central blood temperature, when the head is exposed to a drastically different environment than that of the core. In order to minimize temperature fluctuations within the aural cavity, the opening may be sealed with wax or the temperature of the outer ear may be clamped by a servocontrolled heater (Keatinge and Sloan, 1975).

It seems that esophageal temperature is the preferred site of core temperature measurement. However, accuracy and 'conveniency' may suffer from the complexity of correctly locating the temperature sensitive ending within the esophagus.

Whereas rectal temperature probes are not prone to looping, esophageal probes are usually thin, highly flexible, and may loop very easily. Therefore, the depth of insertion within the esophagus may not necessarily be proportional to the length of probe inserted beyond the nostril. Brengelmann et al. (1979) have proposed an electrocardiographic method of verifying the position of the thermosensitive ending by using the esophageal probe as the positive electrode and placing the negative electrode on the right shoulder. With this technique one can monitor changes in ECG recordings as the depth of insertion is varied. It is thus possible to ascertain when the probe reaches the mid-atrial level within the esophagus. Although the probe designed by Brengelmann et al. (1979) allows for simultaneous recording of temperature and electrocardiogram, the construction of the probe is quite complex and relatively expensive, as it involves placing a thermistor within the tip of the probe.

II. Method

This paper outlines the construction and evaluation of an esophageal probe, similar to that proposed by Brengelmann et al. (1979), but utilizing thermocouple wire.

Size 36, teflon coated copper-constantan thermocouple wire (Omega Engineering Inc.) was fed through radioopaque polyethylene tubing (Cook-Bloomington, Inc.) having an inside diameter of 1.14mm. and an outside diameter of 1.57mm. The copper-constantan thermocouple wire protruding from the polyethylene tubing was threaded through a 5mm piece of 18 gauge stainless steel needle stock. The end of the stainless steel needle piece was welded closed in such a manner, that the thermocouple junction was at the weld tip. The weld created a smooth spherical tip, which aided penetration through the nasal pharynx upon insertion. The tip of the esophageal probe is shown in Fig. A2.1.

In order to locate the position of the probe within the esophagus, it was connected to the positive terminal of an electrocardiograph. The negative terminal of the ECG was connected to a pre-gelled surface electrode located at the right chest. The electrode was placed on the mid-axillary line at the level of the fifth intercostal spacing. When the probe was properly positioned according to the ECG trace, the electrocardiograph was disconnected from the thermocouple wire,

Fig. A2.1 : Constructional details of the temperature sensitive
ending of the esophageal probe.
   A – polyethylene coating of thermocouple wire
   B – teflon coating
   C – copper/constantan wire
   D – radio opaque polyethylene tubine (i.d. = 1.14 mm. and
   o.d. = 1.57 mm.)
   E – 5 mm. piece of 18 gauge stainless steel needle stock.
   F – thermosensitive, welded tip of probe.

C

F

B

A

E

D

282b
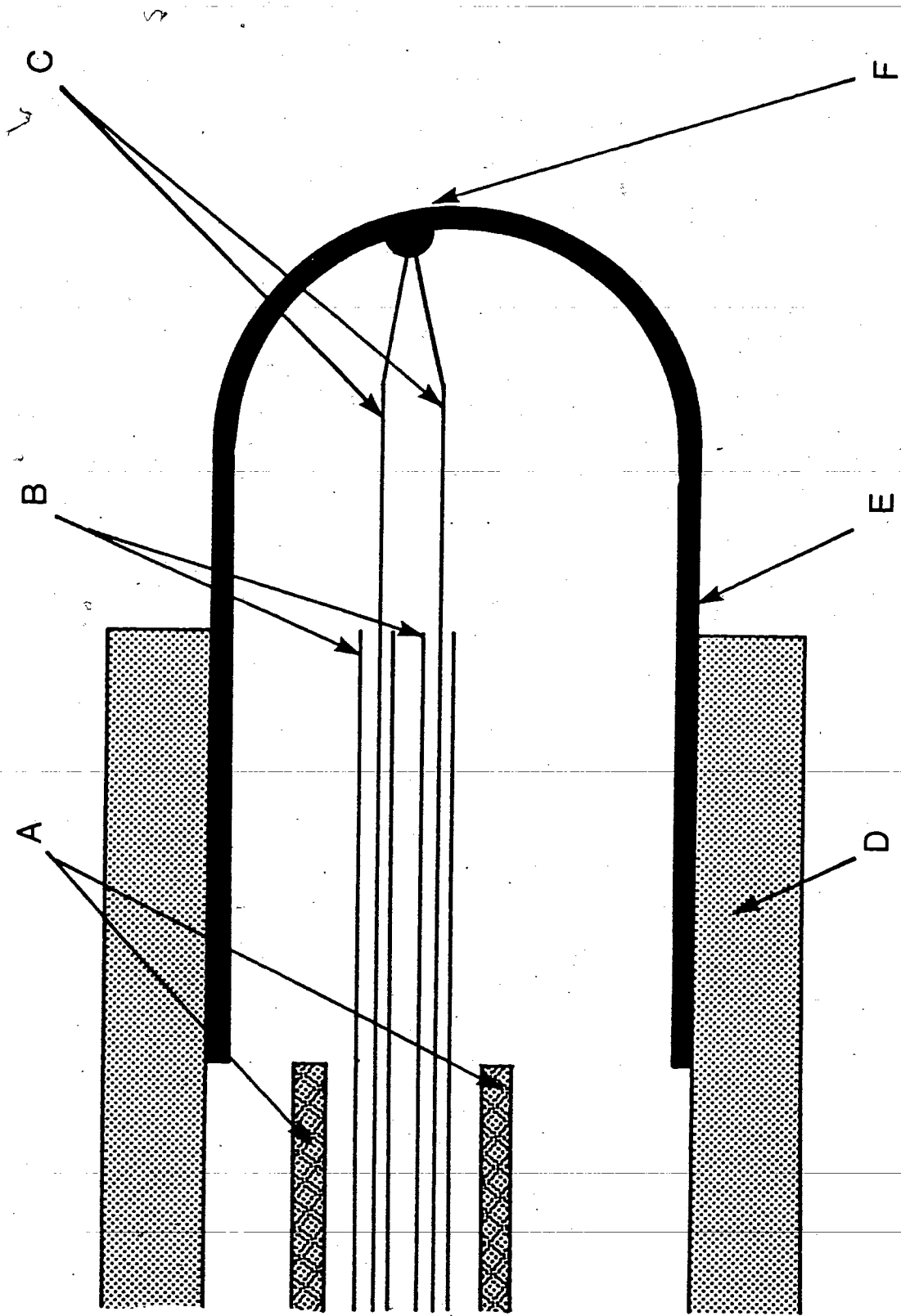
and the thermocouple probe was then connected to a cold junction reference, for temperature measurement.

To verify the change in electrocardiogram with depth of insertion, the probe was inserted at depth of 36, 40, 44 and 48 centimeters from the nostril and the position verified by radiography, as shown in Fig. A2.2.

ECG verification of probe positioning was tested in a series of cold water immersion experiments. As radiographic evaluation was not necessary, regular polyethylene tubing (Intramedic) was used in the construction of the probes. Electrocardiograms were obtained using a Fukuda FD-13 electrocardiogram. Temperatures at the rectal, tympanic and esophageal sites were recorded with a Hewlett-Packard 3497A Data Acquisition system, with internal hardware compensation for the junction temperature.

Fig. A2.2 : Radiographic verification of esophageal temperature
    probe placement at various depths of insertion.
    1) 36 mm.
    2) 40 cm.
    3) 44 cm.
    4) 48 cm.
        Subject is in left lateral position. Temperature
    sensitive ending (B) is located in close proximity of the
    ascending aorta (A) in frame 1, and with increasing depth of
    insertion approaches the level of the apex of the heart (C).
    The black dot situated between the sternum and the heart in
    all the frames is the external pre-gelled negative
    electrode. The ground electrode was placed on the scapula.
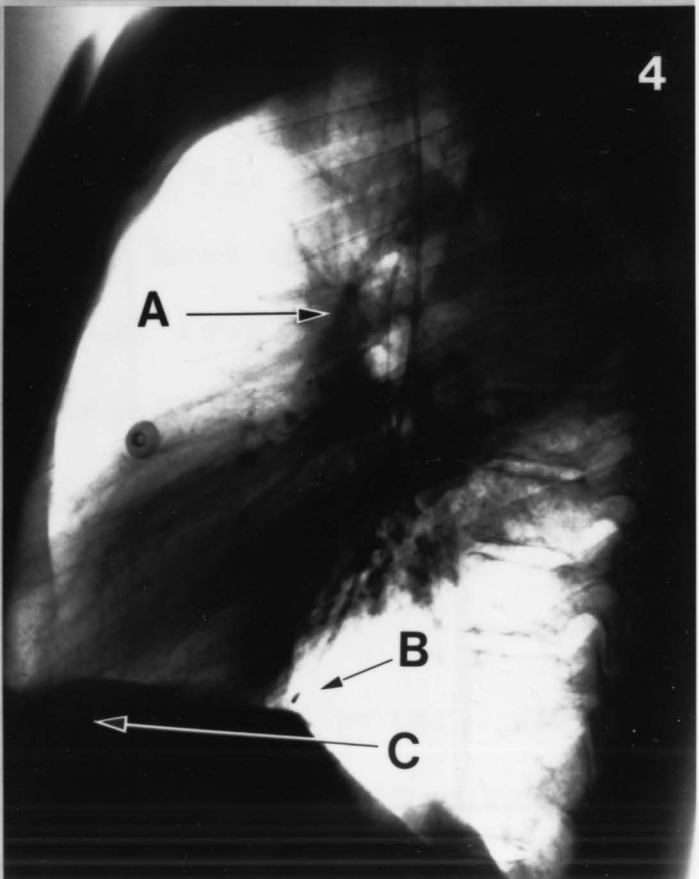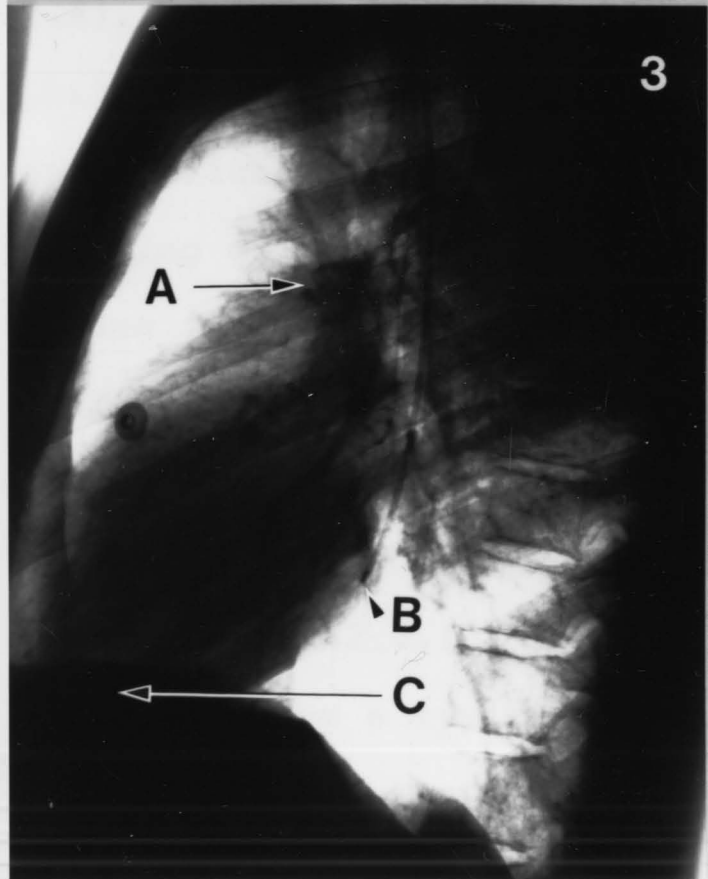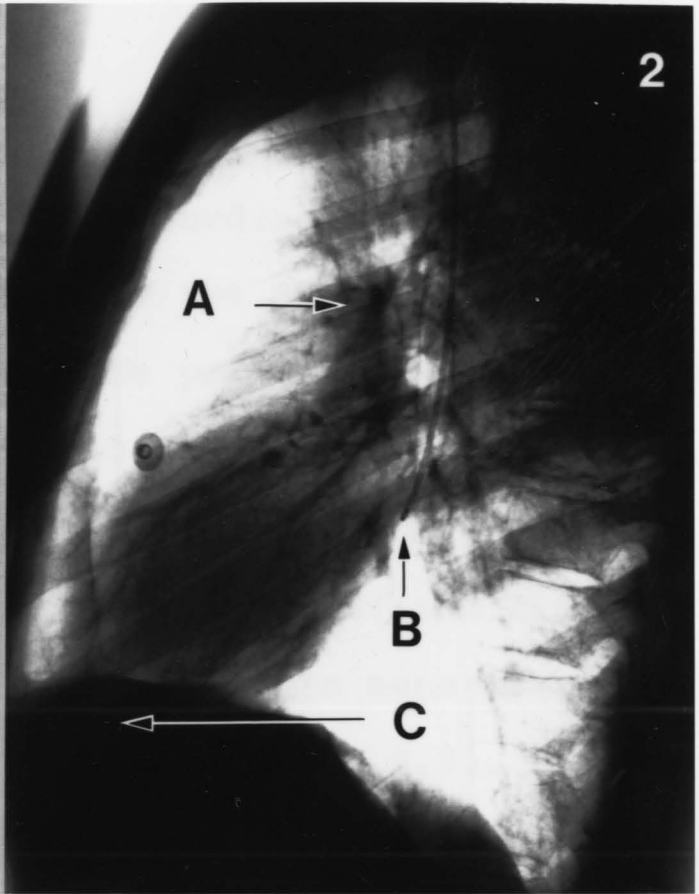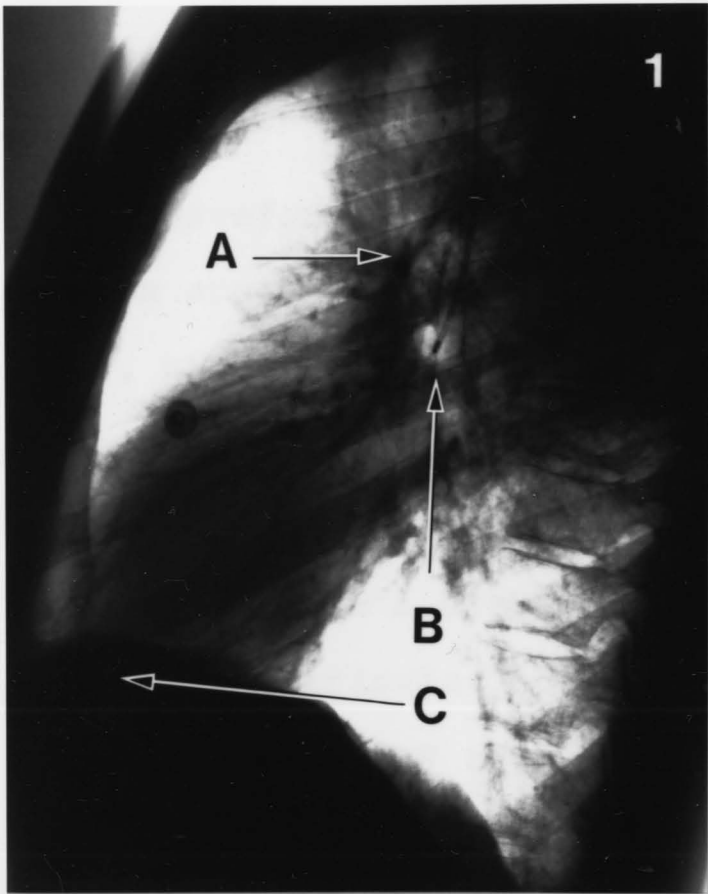
III. Results

The waveforms obtained from ECG recordings at each depth of insertion are shown in Fig. A2.3. Above the atrial level (Fig. A2.2.1), the QRS wave obtained from the positive lead within the esophagus is positive and small in magnitude (Fig. A2.3.1). Approaching the mid atrial level (Fig. A2.2.2), the QRS trace progresses through a biphasic stage (Fig. A2.3.2) and finally, at the atrioventricular border (Fig. A2.2.3), a negative deflection of the QRS trace is observed (Fig. A2.3.3). With further insertion towards the mid ventricular level (Fig. A2.2.4), the QRS maintains a negative deflection but decreases slightly in magnitude, compared to its magnitude at the atrio-ventricular border. Brengelmann et al. (1979) suggest that positioning of the esophageal probe is best determined by examining the P wave. At the mid-atrial level, the esophageal lead will record both positive and negative activity during atrial depolarization. The esophageal probe, they suggest, should be positioned in the region where the P wave is biphasic in nature (Fig. A2.3.1).

Results from a typical immersion in 10° C water, shown in Fig. A.4, indicate that the esophageal temperature agrees closely with tympanic temperature, as confirmed by Hayward et al. (1982) and is maintained at higher levels than rectal temperature (probe inserted 15 cm. beyond the anus).

Fig. A2.3 : Electrocardiographic traces obtained from thermosensitive tip of esophageal probe at various depths of insertion beyond the nostril. Signal was obtained through the thermocouple wire. Anatomical locations of the probe, corresponding to the various depths are shown in Fig.2.

E.C.G.	Depth of insertion (cm.)
1.	36
2.	40
3.	44
4.	48

1 sec.

286b
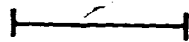
Fig. A2.4 : Results of cold water immersion trial using the
esophageal probe, placed at the mid atrial level.
Tc - core temperature closed circles indicate rectal
temperature, open triangles the esophageal temperature and
crosses, the tympanic temperature.

287a

287b
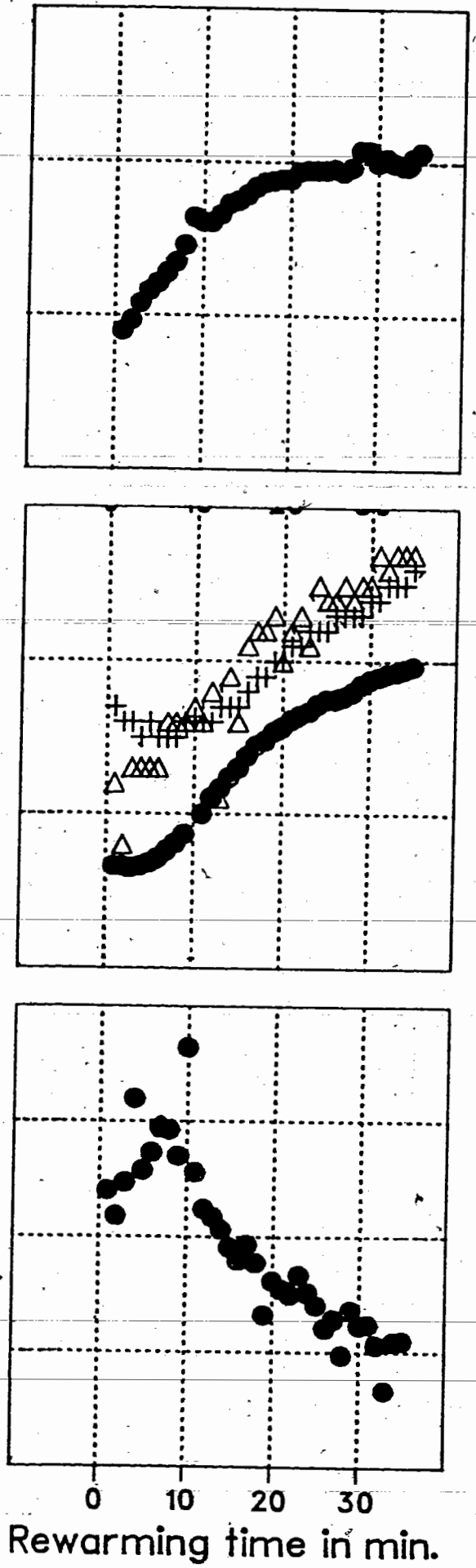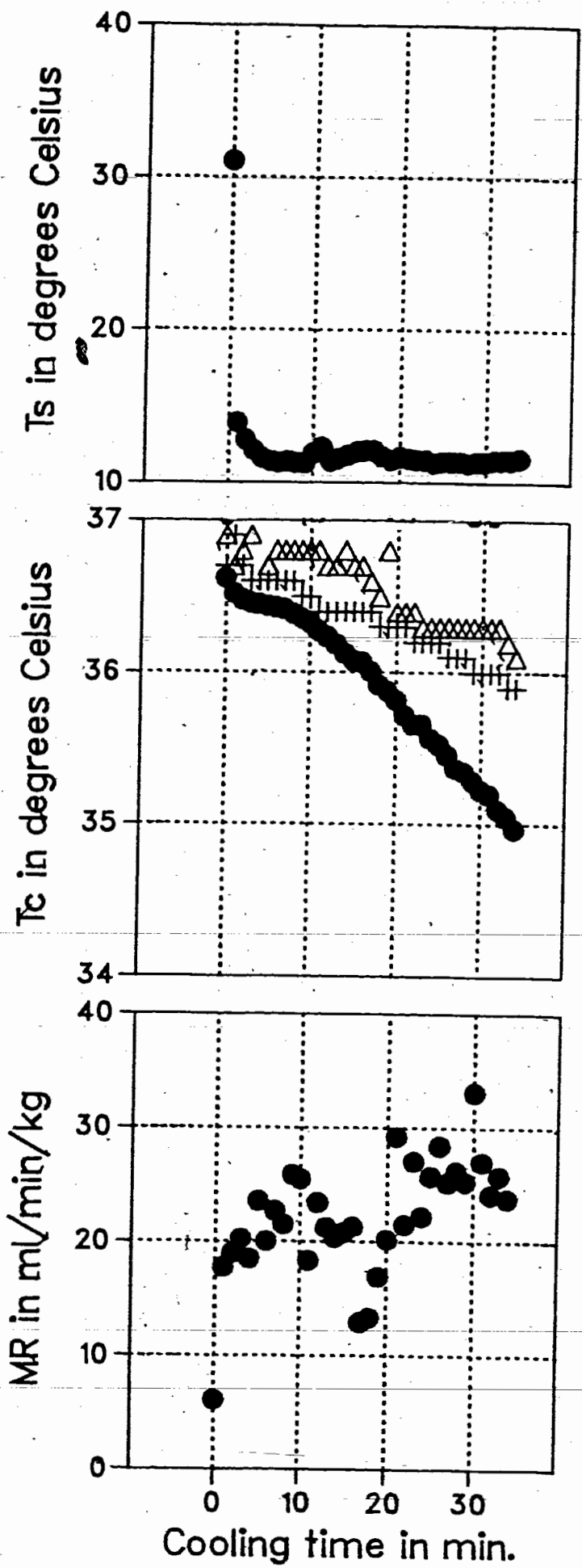
IV. Discussion

The mid atrial level of the heart provides a region of 5-7 cm. where the left atrium and esophagus are in close proximity (Brengelmann et al., 1979). If an error of a few centimeters occurs in positioning the probe, it would still be in close proximity of the atrium anteriorly and the aorta posteriorly.

The results presented support the view of the esophagus being an important site of core temperature measurement and add to the controversy of other reports as to whether rectal temperature is usually maintained at a higher level than esophageal or tympanic temperature (Eichna et al., 1951, Cooper and Kenyon, 1957; Molnar and Read, 1974).

With the present arrangement for measuring esophageal temperature, it is not possible to simultaneously record electrocardiographic traces. This could be achieved with the corporation of a selector switch, which would enable the reading of either temperature or ECG. However, the construction of the probe is simple and economical. The measurement is reliable in most environments, and it reflects more accurately the faster transients of central core temperature.

V. References

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APPENDIX III. : A Comparison of Core Temperature Responses as

Measured in the Rectum, Esophagus and Tympanum during Cold Water

Immersion and Rewarming in Humans

I. Introduction

The necessity for standardized core temperature measurements within the human body, has been emphasized in Appendix II. However, until such stricter standards are formulated, thermoregulatory studies will continue to utilize a variety of core sites as an indication of core temperature. Unfortunately, temperatures measured at different sites within the body are not interchangeable. Furthermore, depending on the protocol of the study, the responses of a set of core temperatures (in the event that more than one core temperature is being monitored) may vary under experimental conditions.

The preferred sites of core temperature measurements are at the tympanum, in the esophagus and rectum. There are opposing views as to the responsiveness and relative magnitudes of core temperatures measured at these sites. Some investigators have found rectal temperature to be higher than blood (Eichna et al., 1951), stomach (Molnar and Read, 1974) and esophageal temperature (Cooper and Kenyon, 1957). However, the above studies utilized a variety of thermal stimuli under different experimental conditions.

Since rectal temperature varies with depth of insertion of the probe beyond the anal sphincters (Mead and Bonmarito, 1949; Behnke and Yaglou, 1951) and tympanic temperature is influenced by the head skin temperature (McCaffrey et al., 1975), there may

exist discrepancies between studies when comparative statements are made based on core temperature.

The present study compares the responses and relative magnitudes of rectal, esophageal and tymapnic temperatures, under a variety of peripheral and core thermal stimuli.

II. Method

A detailed description of the methodology for the present study has been reported earlier in Section C. Briefly, it involved immersing volunteer subjects in water at temperatures of 10°, 15° and 20° C while inhaling air at either room temperature or heated to 40° -45° C and saturated with water vapour. The subjects were removed from the water bath, when their rectal temperature decreased to 35° C or after one hour of immersion, and then rewarmed. During the rewarming period, subjects were placed in a sleeping bag and monitored for 30 minutes, after which they were rewarmed in a jacuzzi.

Core temperature was measured with a YSI 401 thermistor inserted 15 cm. beyond the anus, a thermocouple inserted in the esophagus at the level of the atria (see Appendix II. for details) and a thermocouple inserted in the aural cavity. During the immersion and rewarming periods, the temperature probes were secured with water waterproof tape and therefore the depth of insertion did not vary. The aural cavity was isolated from the external environment with cotton and waterproof tape.

Measurements of core temperature were made every minute with a Hewlett-Packard 3497A Data Acquisition System.

III. Results

The data obtained during the cooling and rewarming period are presented in Table A3.1.

Using a one-tailed t-test for repeated samples, pre-immersion values of esophageal temperature were found to be significantly higher than rectal (p < 0.001) and tympanic (p < 0.02) temperatures. Resting rectal and tymapnaic temperatures were not significantly different in the present study.

During a five minute pre-immersion rest period, inhalation of warm air saturated with water vapour, did not increase the core temperature significantly, when compared to levels observed during rest periods, when subjects were inhaling air at room temperature.

Analysing the data of all subjects for immersion in 10°, 15° and 20° C water, it was found that the cooling rate of rectal temperature was greater than esophageal temperature cooling rate (p < 0.09), when the inhalate was room temperature air. The difference between cooling rates of esophageal and tympanic temperature was not significant in these conditions. Donation of heat to the thorax by way of heated and humidified inspired air, decreased the cooling rate of esophageal temperature (p < 0.01), but did not affect rectal or tympanic temperature.

To assess the effect of heat donation to the thorax, during immersion, on core cooling rates, a paired sample comparison was

Table A3.1 : Comparison of cooling rates at rectal, esophageal and tympanic sites during cold water immersion, with and without donation of heat to the respiratory tract.

Core cooling rates (^{O}C/minute)

Water temp. (^{O}C)	Subj.	N			W		
		$\frac{\Delta Tr}{\Delta t}$	$\frac{\Delta Te}{\Delta t}$	$\frac{\Delta Tt}{\Delta t}$	$\frac{\Delta Tr}{\Delta t}$	$\frac{\Delta Te}{\Delta t}$	$\frac{\Delta Tt}{\Delta t}$
10	AL	.0392	.0316	.0316	.0352	.0217	.0317
	BC	.0336	.0356	.0356	.0162	.0086	.0121
	DS	.0345	.0054	.0089	*	.0033	.0
	DT	.0485	.0235	.0235	.0225	.0083	.033
	RH	.0812	.0788	.0727	.0788	.0833	.033
15	AL	.0393	.0122	.0224	.0208	.0117	.0167
	BC	.0035	.0283	.005	.0068	.0	.0083
	DS	.0188	-.005	-.003	.0018	.0017	.0
	DT	.0131	.0049	-.0016	.0112	.0017	.005
	RH	.0506	.0606	.0394	.0842	.0526	.0316
20	AL	*	.0133	.01	.0153	.0083	.0117
	BC	.0053	*	.0067	.0095	-.0017	.0067
	DS	.0159	.0035	.0035	.0067	.005	.0067
	DT	.0138	.0131	.0131	.0132	.0083	.01
	RH	.048	.0433	.0233	.0312	.02	.015

N   -- denotes experiments where the inhalate was air at room temperature .

W   - denotes experiments where the inhalate was warm air (40° - 45° C) saturated with water vapour.

ΔTr   - change in rectal temperature over the cooling period (Δt).

ΔTe   - change in esophageal temperature over the cooling period (Δt).

ΔTt   - change in tympanic temperature over the cooling period (Δt).

*   - probe slipped

made by combining the core temperature transients during each condition for all subjects. Humidifying and heating the inspired air was observed to significantly decrease the overall cooling rate of core temperature ($p < 0.005$).

An analysis of rewarming data (Table A3.3) revealed, that during passive rewarming (shivering thermogenesis) breathing room air, esophageal temperature had the fastest recovery rate, when compared to tymapnic temperature ($p < 0.02$) and rectal temperature ($p < 0.001$). Inhalation rewarming was observed to benefit only esophageal temperature. Rectal and tympanic temperatures continued to have a negative gradient during the rewarming period.

Table A3.3 : Comparison of rewarming rates at rectal, esophageal
and tympanic sites, during passive and active core
(inhalation) rewarming.

Core rewarming rates (°C/minute)

Water temp. (°C)	Subj.	N $\frac{\Delta Tr}{\Delta t}$	N $\frac{\Delta Te}{\Delta t}$	N $\frac{\Delta Tt}{\Delta t}$	W $\frac{\Delta Tr}{\Delta t}$	W $\frac{\Delta Te}{\Delta t}$	W $\frac{\Delta Tt}{\Delta t}$
10	AL	.0164	−.0256	.0026	−.0033	−.013	.023
	BC	−.0561	−.0581	−.0677	−.008	*	−.18
	DS	−.025	−.0167	−.0067	*	−.02	−.01
	DT	−.0374	−.0429	−.0257	−.0003	−.034	−.0289
	RH	−.0013	*	−.0167	.0084	−.087	*
15	AL	.0152	−.0048	−.0024	−.0117	−.013	.003
	BC	.0146	*	.0036	.0123	.0067	.003
	DS	.0267	−.0133	.03	.0123	0.0	.0133
	DT	−.0127	−.043	−.02	−.0003	−.02	−.01
	RH	.0123	−.04	−.01	*	−.0343	−.0143
20	AL	*	0.0	.0167	.0143	.0067	.0167
	BC	.0103	*	.0133	.0085	−.0039	.0154
	DS	.0083	*	*	.0137	*	.023
	DT	.0017	−.02	−.0067	.0095	−.01	0.0
	RH	.0056	−.02	.012	.002	−.0267	.0067

N – denotes experiments where the inhalate was air at room temperature

W – denotes experiments where the inhalate was warm air (40° – 45° C) saturated with water vapour.

ΔTr – change in rectal temperature over the rewarming period (Δt).

ΔTe – change in esophageal temperature over the rewarming period (Δt).

ΔTt – change in tympanic temperature over the rewarming period (Δt).

* – probe slipped

IV. Discussion

Present data suggest that during rest, esophageal temperature is maintained higher than rectal or tympanic temperature. During the cooling in cold water, rectal temperature exhibits the fastest cooling rate, whereas the cooling rates of esophageal and tympanic temperatures are similar (the difference was not significant). In an unpublished study, Hayward (1982) measured rectal, esophageal, tympanic, gastric and pulmonary arterial blood temperature, during cooling and several methods of rewarming. He found that the best correlates of the temperature of the blood in the pulmonary artery were esophageal and tympanic temperature. The results of this study tend to agree with those of Hayward (1982) regarding relative rates of change of core temperatures.

Donation of heat to the respiratory tract significantly reduced the cooling rates of esophageal and tympanic temperature, but did not affect the response of rectal temperature. Since the heat is being transferred directly to the blood perfusing the alveoli in the lungs, this finding would suggest a relatively decreased heat transfer to the gastrointestinal region. It has been suggested that the hydrostatic pressure causes a shift in blood volume towards the thoracic region (West, 1979). This coupled with a decrease in splanchnic blood flow during hypothermia (Brauer et al., 1959),

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may to an extent also explain the greater responsiveness of rectal temperature during periods of cooling. Since thoracic blood volume increase and perfusion of the hypothalamus is not altered, a strong correlation of esophageal and tymapnic temperature would be expected.

During periods of passive and active rewarming, esophageal temperature had a significantly faster recovery rate than rectal and tympanic temperatures. The present study does not indicate improved recovery rates of core temperature, when inhalation rewarming is used. However, Morrison et al. (1980) suggest that core temperature at the onset of rewarming should be taken into account, if such comparative statements are to be made. They suggest the following relationships between rewarming rates and initial body temperatures :

$$\emptyset r = 50.85 - 1.29 * Tor - 0.16 * Tos \qquad \text{...(A3.1)}$$
$$\emptyset t = 54.37 - 0.66 * Tot - 0.69 * Tor \qquad \text{...(A3.2)}$$

where,

$\emptyset r$ = rate of rewarming of rectal temperature, dTr/dt ($^{\circ}C/min.$).

$\emptyset t$ = rate of rewarming of tympanic temperature, dTt/dt ($^{\circ}C/min.$).

Tor = rectal temperature at onset of rewarming.

Tot = tympanic temperature at onset of rewarming.

Tos = mean skin temperature at onset of rewarming, obtained from

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chest and calf sites.

Indeed, the initial core temperatures during rewarming were substantially higher during experiments where subjects inspired warm moist air during cooling in cold water.

Subjective observations during the rewarming period indicate that inhalation rewarming supressed the intensity of the shivering tremor; by doing so, the magnitude of shivering thermogenesis is also decreased. It would appear therefore, that the thermal energy donated to the core was not substantially greater than that which was suppressed, by virtue of the inhibition of shivering thermogenesis.

The present results do not confirm the results of Molnar and Read (1974), which suggest that rectal temperature is greater than blood temperature, assuming esophageal temperature is a good correlate of arterial blood temperature. However, their measurements were made within the extracorporeal circulation and not in vivo, and it is possible that blood temperature may have decreased slightly in the extra-corporeal circulation. Cooper and Kenyon (1957) also recorded higher temperatures within the rectum compared to temperatures in the esophagus. However, their subject was anaesthetized and undergoing open chest surgery, which would make comparisons with the present study unjust.

Observations on the advantages and disadvantages of different core temperature sites are summarized in Table A3.4. The present study indicates a good correlation in the responsiveness of esophageal and tympanic temperature and suggests that rectal temperature alone is not an adequate measure of the thermal state of the body core, if the body core temperature is to indicate the status of the myocardium and central nervous system.

Table A3.4 : Evaluation of core temperature sites.

COMMENT

Intra-muscular

Invasive; causes slight discomfort and is not considered core temperature.

Tympanic

Easy to use; measurements affected by head skin temperature; susceptible to poor sealing of external auditory meatus.

Rectal

Sensitive to depth of insertion variations; not good for exercise conditions, especially running; remote from 'central' core volume.

Esophageal

Not sensitive to peripheral temperatures or small variations in depth of insertion; can be fixed firmly; depth can be verified electrocardiographically; correlates well with pulmonary arterial blood temperature; may be unstable in cold air environments (<0° C).

V. References

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APPENDIX IV. : Cardiovascular Responses to Prolonged Immersion

in Cold Water and to Rewarming in Humans

I. Introduction

Sudden immersion in cold water induces a notable transient response in heart rate (Hayward et al., 1977; McKay, 1972). The most prominent instigators are anxiety, temperature sensation and in the case of extremely cold water (<15° C) sensation of pain. Cold water immersion results in increased thermogenic drive, indicated by elevated levels of oxygen consumption (see section D). Initially there is a transient response followed by a return to levels slightly higher than pre-immersion values. During prolonged cold water immersion there is a progressive rise in metabolic heat generation.

As outlined by Raven et al. (1970), there has been an emergence of opposing observations on the response of heart rate due to prolonged cold water immersion. Evidence of McKay (1972) and Raven et al. (1970) suggests slight elevation of heart rate during prolonged cold exposure. Variations observed by McKay (1972) in water at 4.6°, 10.5° and 18.2° C were more prominent than those reported by Raven et al. (1970), who studied responses of individuals exposed to a cold air environment of 5° C.

Counteracting the metabolic excitatory stimulus, is the inhibitory effect of cooling of the cardiac muscle (Furukawa et al., 1979; Goldberg, 1958; Ledsome et al., 1981), spinal cord (Walther et al., 1970) and skin (Rowell et al., 1969) on heart

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rate. It is difficult to partition the contributions of excitatory and inhibitory stimuli on heart rate during cold exposure in humans. There has been a tendency to quantify the inhibition due to a drop in cardiac muscle temperature, by observing the effect of changes in rectal temperature on heart rate and oxygen consumption. Although this site is favoured for evaluating core temperature, due to ease of measurement, the temperature is not indicative of cardiac muscle temperature. Unpublished data of Hayward (1982) indicate that esophageal temperature is the best indicator of pulmonary arterial blood.

The present study investigates the relationship between heart rate and oxygen consumption during immersion in three different bath temperatures, while accounting for the contribution of changes in esophageal temperature. The heart rate response to a thermogenic stimulus is also compared to the heart rate response resulting from an exercise stimulus.

II. Methods

Five male university students participated in the study.
Each subject underwent six immersion trials and a submaximal
exercise test. On separate occasions, subjects were immersed in
water at a temperature of 10°, 15° and 20° C. One series of
immersion trials entailed the subjects inhaling air at room
temperature, while during a second series of immersions in
identical water temperatures, the inhalate was warm air (40° to
45° C) saturated with water vapour.

During the exercise condition, subjects performed a graded
exercise on an electrically braked bicycle (Quinton Instruments
Ltd.). Each level of exercise was maintained for five minutes to
allow for stabilization of heart rate and oxygen consumption.

Details of the experimental arrangement and of the methods
of acquisition of physiological data have been outlined in
section D. Esophageal temperature was recorded with a
thermocouple probe located at the level of the atria, as
suggested by Brengelmann et al. (1979; see also Appendix II. of
this thesis).

Subjects were monitored continuously throughout the cooling
and rewarming period and data was collected at minute intervals.

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III. Results

The heart rate response to cold water immersion followed a similar pattern for all subjects. A representative example of the heart rate response, for one subject, is depicted in Fig. A4.1. The initial transient response, at the onset of immersion, decays to levels slightly above resting values. The magnitude of the overshoot in heart rate response seems partly due to the peripheral thermal stimulus. As observed in Fig. A4.1, the magnitude of the transient response is greater for immersions in 10° and 15° C water than for the immersion in 20° water. For this particular subject, the initial heart rate response is slightly greater for the immersion in 15° C water. In general, the transient response to immersion in 10° and 15° C water were similar for all subjects. The onset of the heart rate overshoot coincides with the initial transient response in thermogenesis, as indicated by the oxygen consumption (VO2 in ml. O2/min./kg.) in Fig. A4.1.

After eighteen minutes of immersion there is a gradual increase in thermogenesis, which is not reflected by the heart rate response. In 10° C water, the heart rate is maintained fairly constant at levels above resting, while in 15° and 20° C water, the heart rate decays and oscillates about resting levels, respectively. On rewarming from mild hypothermia (end immersion rectal temperature of 35° C), a substantial transient

Fig. A4.1 : Heart rate and oxygen consumption responses of
subject AL during immersion in 10°, 15° and 20° C water.

309b
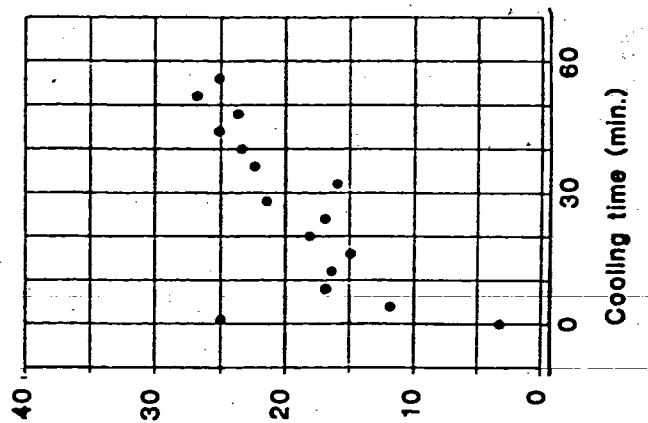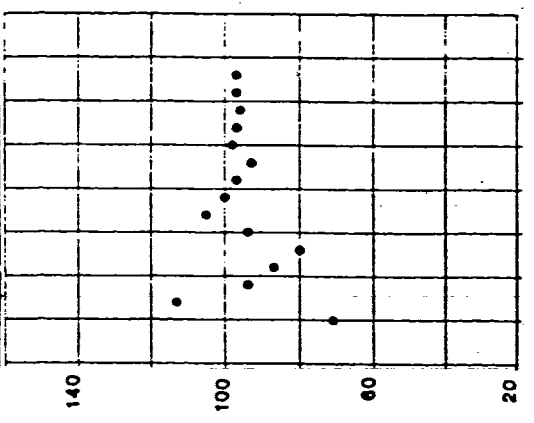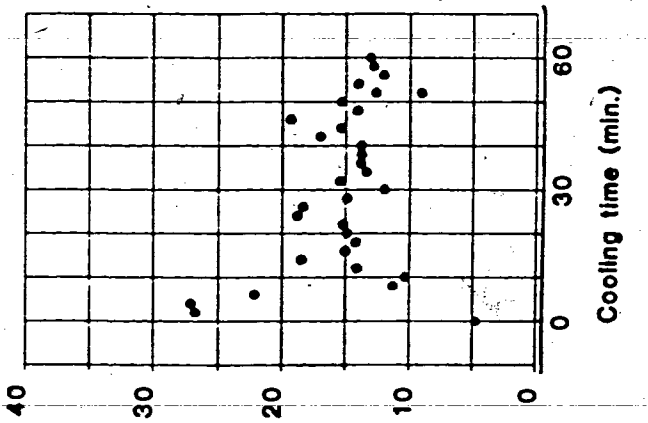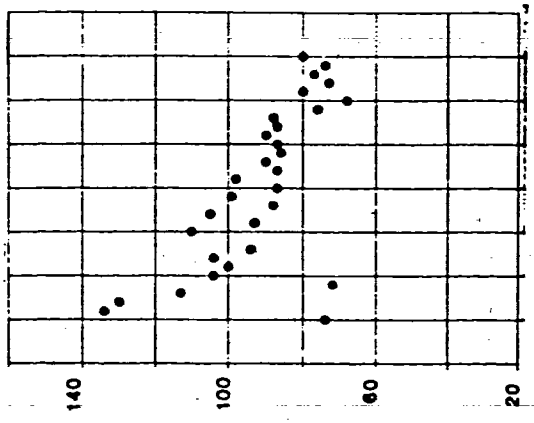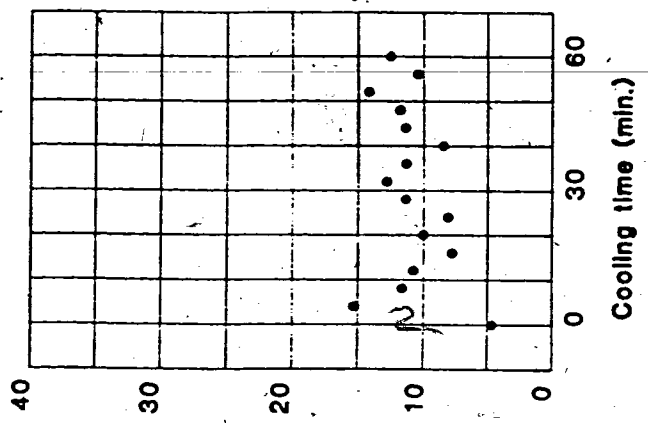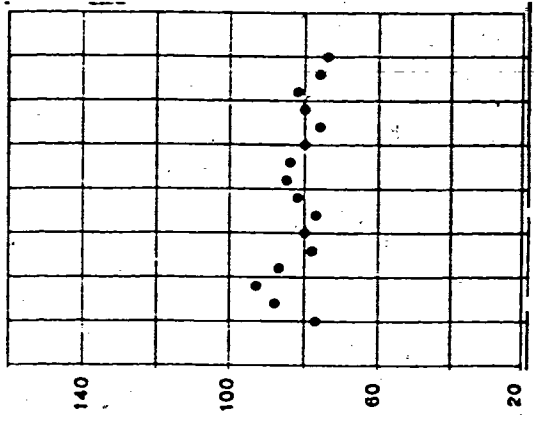
response is observed after emergence from 10° C water and is not evident in the rewarming periods following immersion in 15° and 20° C water. On the contrary, rewarming following immersion in 20° C water instigated a profound bradycardia during the initial ten minutes of rewarming for subject AL, depicted in Fig. A4.2.

The lack of responsiveness of heart rate to the overall thermogenic drive becomes apparent in Fig. A4.3. Despite seven-fold elevations in oxygen consumption from resting levels of 4 ml. O2/min./kg. to 30.1 ml. O2/min./kg., heart rate is maintained within limits of 60 to 84 beats/minute, during immersion in 10° C water and between 45 and 70 beats/minute during rewarming.

For comparative purposes, the response to a submaximal exercise stimulus is plotted in Fig. A4.3. The plotted values were obtained at the end of each five minute exercise period. For a range of values between resting and 170 beats/minute, there was a linear relationship between oxygen consumption and heart rate. Only a portion of the derived regression line is plotted in Fig. A4.3. It is evident, that the increased demands for oxygen during cooling and rewarming were not met with elevated heart rates, as observed during the exercise stimulus.

Fig. A4.4 illustrates that the major stimulus for thermogenesis is derived from core temperature. There is a curvilinear increase in metabolic heat production with decreasing esophageal temperature. During rewarming, however, the thermogenic drive decreases despite decreased esophageal

Fig. A4.2 : Heart rate and oxygen consumption responses of subject AL during rewarming after immersion in 10°, 15° and 20° C water.

311a

Rewarming time (min.)

Rewarming time (min.)

Rewarming time (min.)

Heart rate (beats/min.)

$\dot{V}O_2$ (ml./kg./min.)

311b
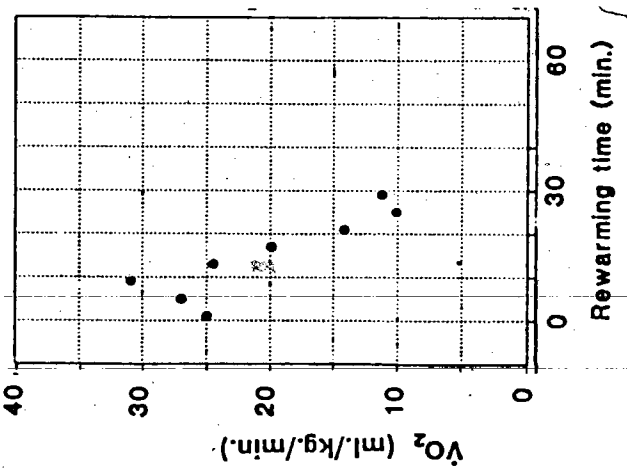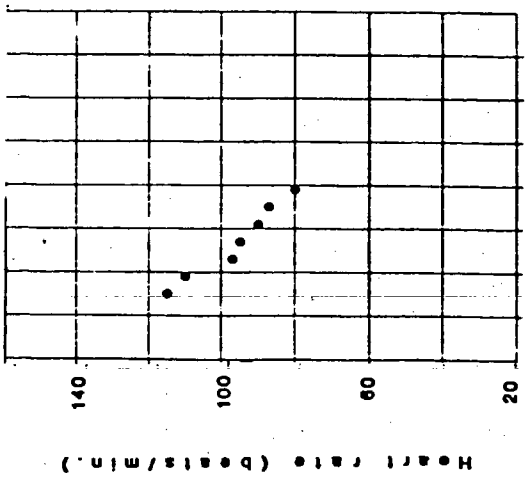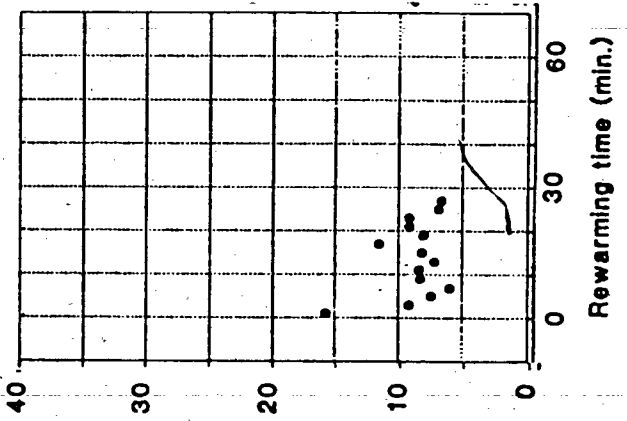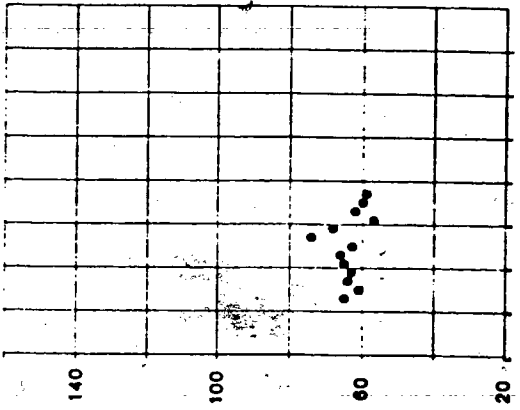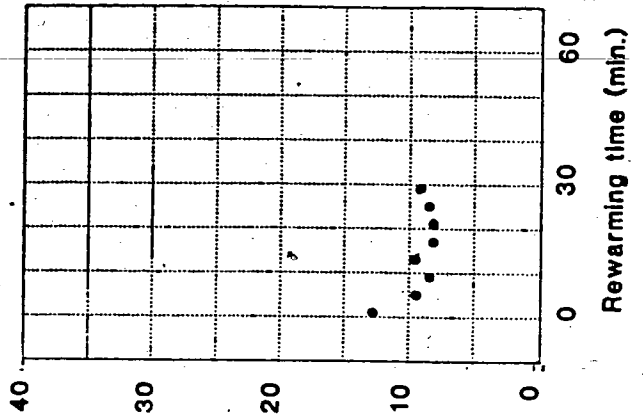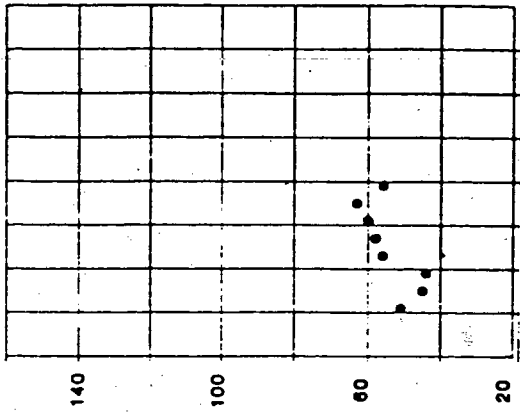
Fig. A4.3 : Comparison of the relationship between heart rate
and oxygen consumption during cold water immersion and
submaximal exercise.

Heart rate (beats/min.)

Oxygen consumption (ml. O_2/kg./min.)

T_{water}

10°C

15°C

20°C

312b
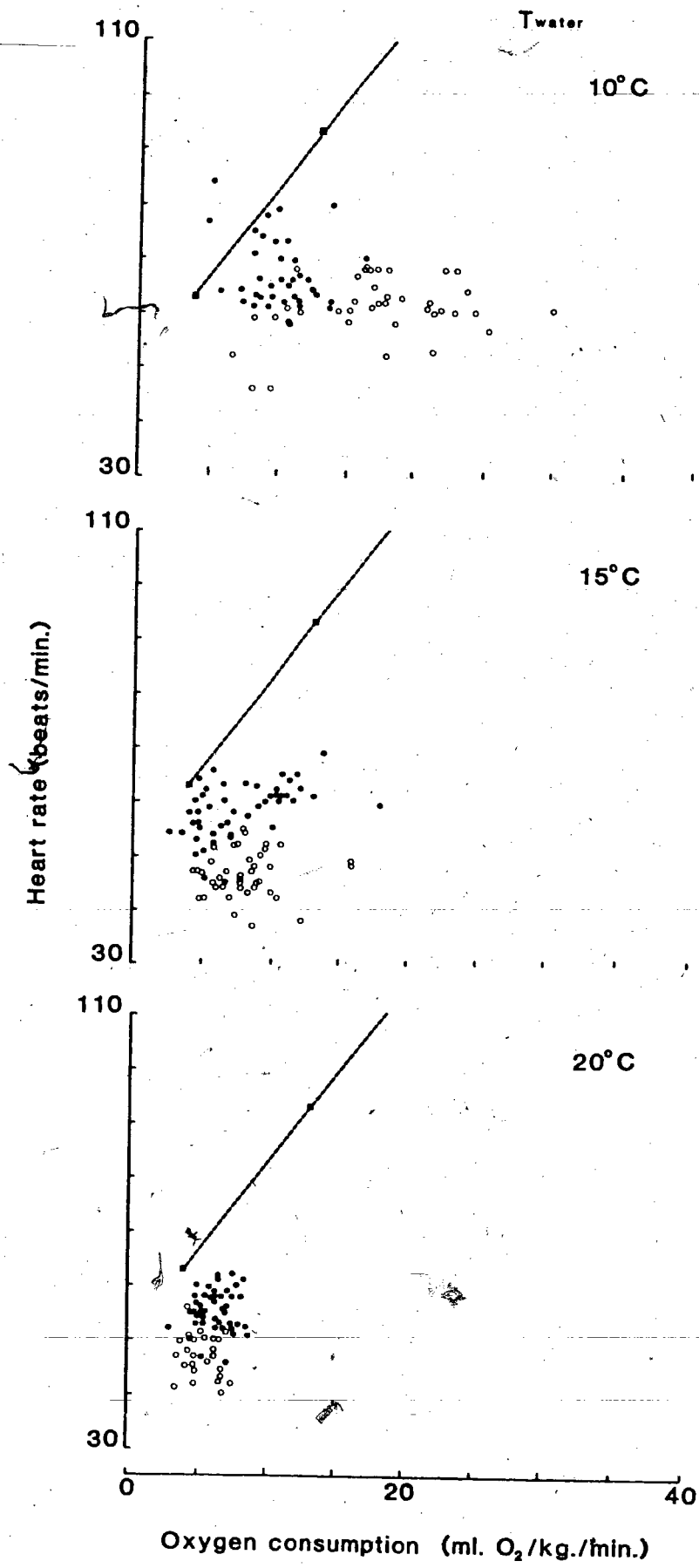
Fig. A4.4 : The effect of esophageal temperature on oxygen
consumption and heart rate during immersion in 10° C water.

313a

Esophageal temperature (°C)

313b
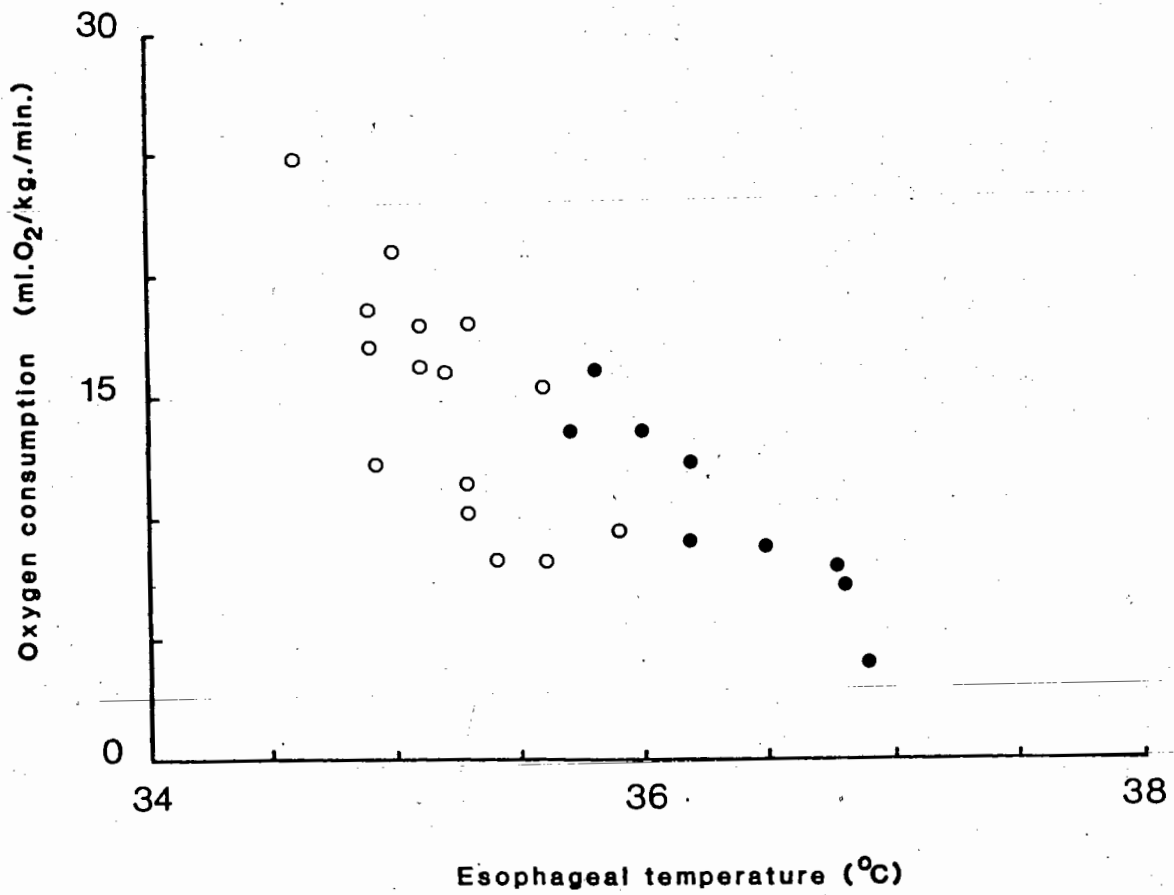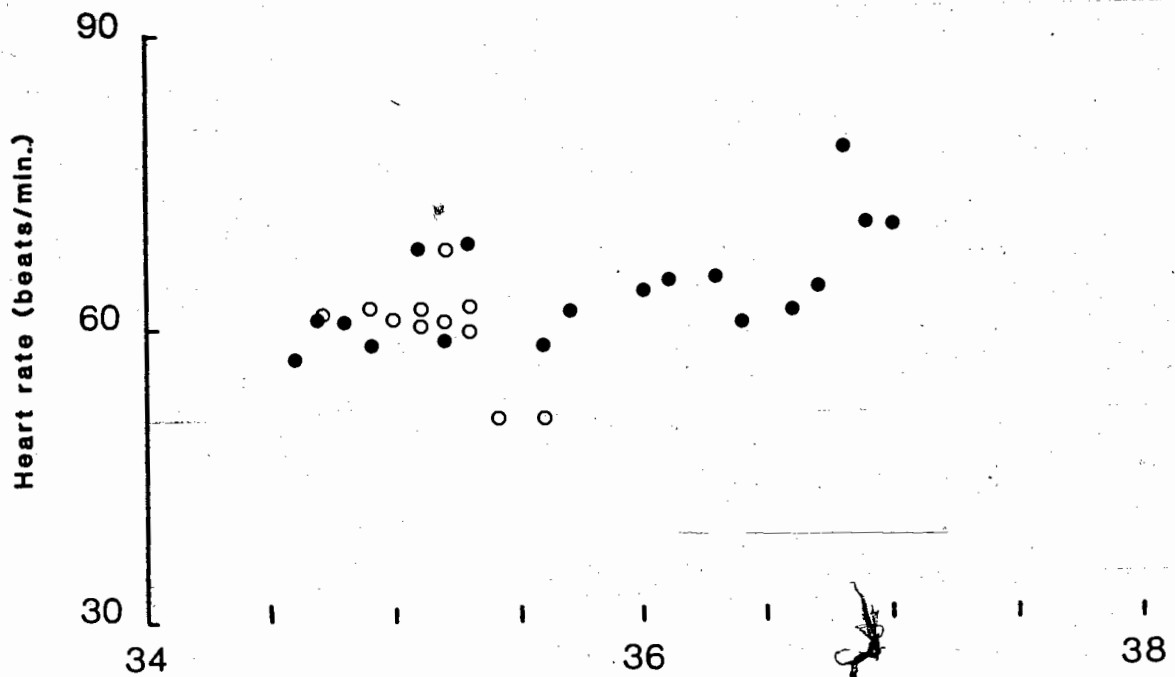
temperature. For the range of esophageal temperatures investigated, there appears to be no effect on heart rate, due to esophageal temperature _per se_.

The heart rate responses during immersion and rewarming trials, where the inhalate was warm saturated air, are similar to the responses observed in trials where room temperature was inhaled. Donation of heat to the core region did not affect the initial transient response to sudden immersion. The most prominent feature of these latter trials, as discussed in section D, is an inhibition of thermogenesis, which results in variations of oxygen consumption within much narrower limits for each water temperature than depicted in Fig. A4.3.

IV. Discussion

Decreasing central and core temperatures results in progressively elevated levels of shivering thermogenesis (Benzinger, 1969; Craig and Dvorak, 1966; section D of this thesis). The effect of decreasing cardiac muscle temperature however, is an inhibition of heart rate (Furukawa et al. (1979); Goldberg, 1958; Ledsome et al. (1981). During an exercise stimulus, increases in oxygen consumption are reflected by an increase in heart rate (Ekblom et al., 1971). Whole body cooling therefore, results in opposing stimuli on heart rate; the excitatory effect of increasing shivering thermogenesis and inhibitory effect due to decreasing cardiac muscle temperature.

Although the results depicted in Fig. A4.4 illustrate the stimulation of thermogenesis with decreasing core (esophageal) temperature, the effect on heart rate is not evident. It is possible that, in the absence of a thermogenic drive, bradycardia would result from the decreased cardiac muscle temperature. However, the increasing metabolic demands of shivering muscle acts to elevate heart rate. The heart rate response observed in Fig. A4.4 is, therefore, the result of a superposition of temperature and metabolic effects.

The differences in heart rate response to exercise and shivering thermogenesis are substantial (Fig. A4.3). Assuming a similar cardiac output for both conditions, it is evident from Fig. A4.3, that at an oxygen consumption of 20 ml.O2/kg./min.

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during immersion in 10° C water, there would have to be a nearly two fold increase in stroke volume, since the heart rate is approximately half of that observed during the exercise stimulus.

Cardiovascular parameters of cardiac output and stroke volume were not monitored in present study. However, marked differences in stroke volume during exercise in air and water (18°, 25° and 33° C) have been observed by McArdle et al. (1976). From their study it is not evident whether the subjects experienced core cooling. It is very likely that exercise in 18° water generated sufficient metabolic heat for maintenance of normothermia. Their results are therefore not confounded with effects of decreasing core temperature. Nicolas and Nicolas (1974) have shown that accidental hypothermia instigates low cardiac output and stroke volume, as a result of bradycardia.

The majority of the subjects exhibited a profound bradycardia during the rewarming period. As can be seen from Fig. A4.2, metabolic rate remains elevated during the initial period of rewarming and subsequently decreases towards resting levels. During the latter half of rewarming therefore, the thermogenic stimulus is absent. Core temperature however remains at end-immersion values. The bradycardia observed on rewarming may therefore reflect more the influence of cardiac muscle temperature on heart rate.

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APPENDIX V. : Computer Programs

The underlying theories and derivation of the thermoregulatory model are presented in Section E. This section consists of supplementary information for Section E.

I. Predicting the Generalized Neural Response to a Thermal Stimulus in Humans

```
C
C      SUPERPOSITION OF NEURAL CODED TEMPERATURE
C      INFORMATION FROM CORE AND CUTANEOUS
C      THERMORECEPTORS.
C
C
C      THIS PROGRAM ESTIMATES THE RESPONSE OF COLD
C      AND WARM RECEPTORS TO TRANSIENT TEMPERATURE
C      STIMULII (IMPULSES/SECOND).
C
C
C      IGOR B. MEKJAVIC
C      S.F.U., 1982
C
C
C      RESTRICTION: MAXIMUM 200 MINUTE SAMPLES
C
C
C      DIMENSION TIME(200),TR(200),TTY(200),TESO(200),M(200),
C     &X(6000),FT(6000),C(6000),R(6000),E(6000),T(6000),W(6000),
C     &FP(6000),PMR(200),T1(200),T2(200),T3(200),FI(6000),
C     &ARM(200),CHEST(200),THIGH(200),CALF(200),
C     &CA(6000),AS(6000),CC(6000),HS(6000),CT(6000),TS(6000),
```

```
31       &CL(6000),LS(6000),RS(6000),ES(6000),TYS(6000),WAS(6000),
32       &WHS(6000),WTS(6000),WLS(6000),CS(6000),WS(6000),
33       &WA(6000),WH(6000),WT(6000),WL(6000)
34 C
35 C
36        REAL TIME,TR,TTY,TESO,M,T1,T2,T3,X,FT,C,R,E,T,W,
37       &PMR,Y,J3,FI,F,ARM,CHEST,THIGH,CALF,CA,CC,AS,HS,
38       &CT,TS,CL,LS,RS,ES,TYS,WAS,WHS,WTS,WLS,CS,WS,
39       &WA,WH,WT,WL
40 C
41 C     READ TIME (MIN.), RECTAL (T1), ARM, CHEST, THIGH,
42 C     CALF, TYMPANIC (T2) AND ESOPHAGEAL (T3) TEMPERATURES
43 C     FROM RAW DATA FILE
44 C
45 C
46 100   N=1
47 120   READ(1,122,END=180)TIME(N),T1(N),ARM(N),CHEST(N),
48       &THIGH(N),CALF(N),T2(N),T3(N)
49 122   FORMAT(1X,F2.0,10X,F6.3,4F4.1,8X,2F4.1)
50        TR(N)=T1(N)-2.0
51        TTY(N)=T2(N)-2.0
52        TESO(N)=T3(N)-2.0
53        N=N+1
54        GOTO 120
55 180   N=N-1
56 C
57 C
58 C     READ METABOLIC RATE FROM ANALYZED DATA FILE.
59 C     ASSUMPTION BEING MADE IS THAT NUMBER OF SAMPLES
60 C     IS EQUAL TO THE NUMBER OF CASES READ FROM RAW
61 C     DATA FILE.
```

```
62  C
63  C
64  190  DO 195 I6=1,N
65  195  READ (2,197) M(I6)
66  197  FORMAT(32X,F6.3)
67  C
68  C        OUTPUT FROM SKIN COLD RECEPTORS: ARM REGION
69  C
70       Z=1.0
71  200  CALL NEURAL (ARM,CA,N,Z,I5,AS)
72  C
73  C        OUTPUT FROM SKIN COLD RECEPTORS: CHEST REGION
74  C
75  202  CALL NEURAL (CHEST,CC,N,Z,I5,HS)
76  C
77  C        OUTPUT FROM SKIN COLD RECEPTORS: THIGH REGION
78  C
79  204  CALL NEURAL (THIGH,CT,N,Z,I5,TS)
80  C
81  C        OUTPUT FROM SKIN COLD RECEPTORS: CALF REGION
82  C
83  206  CALL NEURAL (CALF,CL,N,Z,I5,LS)
84  C
85  C
86  C        OUTPUT FROM CORE COLD RECEPTORS: RECTAL REGION
87  C
88  C
89  220  CALL NEURAL (TR,R,N,Z,I5,RS)
90  C
91  C        OUTPUT FROM CORE COLD RECEPTORS: ESOPHAGEAL REGION
92  C
```

```
  93    C      240     CALL NEURAL (TESO,E,N,Z,I5,ES)
  94    C
  95    C             OUTPUT FROM CORE WARM RECEPTORS: TYMPANIC REGION
  96    C
  97    C
  98    C
  99    C       .Z=-1.0
 100    C      260  .CALL NEURAL(TTY,T,N,Z,I5,TYS)
 101    C
 102    C
 103    C
 104    C             OUTPUT FROM SKIN WARM RECEPTORS: ARM REGION
 105    C      290     CALL NEURAL (ARM,WA,N,Z,I5,WAS)
 106    C
 107    C             OUTPUT FROM SKIN WARM RECEPTORS: CHEST REGION
 108    C
 109    C      292     CALL NEURAL (CHEST,WH,N,Z,I5,WHS)
 110    C
 111    C             OUTPUT FROM SKIN WARM RECEPTORS: THIGH REGION
 112    C
 113    C      294     CALL NEURAL (THIGH,WT,N,Z,I5,WTS)
 114    C
 115    C             OUTPUT FROM SKIN WARM RECEPTORS: CALF REGION
 116    C
 117    C      296     CALL NEURAL (CALF,WL,N,Z,I5,WLS)
 118    C
 119    C
 120    C
 121    C      NEURAL RESPONSES OF THERMORECEPTORS AT TWO
 122    C      SECOND INTERVALS, AS ESTIMATED BY SUBROUTINE
 123    C      NEURAL.
```

```
124 C
125 C      OUTPUT CONTAINS TOTAL (STATIC AND DYNAMIC) AND
126 C      STATIC NEURAL RESPONSE.
127 C
128 C
129        WRITE(3,300)
130 300    FORMAT(15X,'NEURAL RESPONSES OF THERMORECEPTORS AT ONE ',
131       &'MINUTE INTERVALS, AS ESTIMATED BY SUBROUTINE NEURAL')
132        WRITE(3,302)
133 302    FORMAT('SECONDS',5X,'C',9X,'R',9X,'E',9X,'T',9X,'W',
134       &9X,'CS',9X,'RS',9X,'ES',9X,'TS',9X,'WS')
135        DO 305 I=60,I5,2
136        C(I)=(CA(I)+CC(I)+CT(I)+CL(I))/4.0
137        CS(I)=(AS(I)+HS(I)+TS(I)+LS(I))/4.0
138        W(I)=(WA(I)+WH(I)+WT(I)+WL(I))/4.0
139        WS(I)=(WAS(I)+WHS(I)+WTS(I)+WLS(I))/4.0
140 305    WRITE(3,310)I,C(I),R(I),E(I),T(I),W(I),
141       &CS(I),RS(I),ES(I),TS(I),WS(I)
142 310    FORMAT(I8,10F10.3)
143 C
144 C
145 C      OUTPUT METABOLIC RATE, SKIN AND CORE TEMPERATURES.
146 C      UNIT=4
147 C
148        WRITE(4,380)(M(I),ARM(I),CHEST(I),THIGH(I),CALF(I),
149       &TR(I),TTY(I),TESO(I),I=1,N)
150 380    FORMAT(8F6.3)
151        STOP
152        END
153 C
154 C
```

```
C
C            SUBROUTINE NEURAL
C
       SUBROUTINE NEURAL (X,FT,N,Z,I5,FS)
       DIMENSION X(200),FT(200),DX(200),FP(12000),FI(12000),
      &FS(12000)
       DOUBLE PRECISION Y,F,Y1,Y2
       REAL P
       N1=N*60
       N2=N-1
       Y=X(1)
       IF(Z.LT.0.0) GOTO 1000
       CALL COLD(Y,F)
       GOTO 1005
 1000  CALL WARM(Y,F)
 1005  DO 1010 I=2,100,2
 1010  FI(I)=F
       DO 1500 I1=1,N2
       DX(I1)=(X(I1)-X(I1+1))/30.0
 1030  DO 1500 I2=2,60,2
       I3=I2+40
 1050  IF(DX(I1).GE.0.0) GOTO 1100
       P=-Z
       GOTO 1200
 1100  P=Z
 1200  IF(Z.LT.0.0) GOTO 1300
       Y1=X(I1)
       IF(Y1.LT.12.5)GOTO 1210
       IF(Y1.GT.35.6)GOTO 1215
       GOTO 1220
```

```
186   1210 F=1.0
187        GOTO 1230
188   1215 F=0.0
189        GOTO 1230
190   1220 CALL COLD (Y1,F)
191   1230 F1=F
192        Y2=X(I1)-DX(I1)
193        IF(Y2.LT.12.5)GOTO 1240
194        IF(Y2.GT.35.6)GOTO 1245
195        GOTO 1250
196   1240 F=1.0
197        GOTO 1260
198   1245 F=0.0
199        GOTO 1260
200   1250 CALL COLD (Y2,F)
201   1260 F2=F
202        GOTO 1350
203   1300 Y1=X(I1)
204        IF(Y1.LT.20.0)GOTO 1305
205        IF(Y1.GT.45.0)GOTO 1310
206        GOTO 1315
207   1305 F=0.0
208        GOTO 1320
209   1310 F=1.0
210        GOTO 1320
211   1315 CALL WARM (Y1,F)
212   1320 F1=F
213        Y2=X(I1)-DX(I1)
214        IF(Y2.LT.20.0)GOTO 1325
215        IF(Y2.GT.45.0)GOTO 1330
216        GOTO 1335
```

```
217  1325  F=0.0
218        GOTO 1340
219  1330  F=1.0
220        GOTO 1340
221  1335  CALL WARM (Y2,F)
222  1340  F2=F
223  1350  S=F2-F1
224        A=F1*ABS(S)*5.0
225        B=A+S
226        X1=-2.0
227  1358  DO 1360 I4=I2,I3,2
228        X1=X1+2.
229        FP(I4)=S*(1.0-EXP(-X1/5.5))+P*A*(EXP(-X1/5.5)-EXP(-X1/3.3))
230  1359  FI(I4-2+I1*60)=FI(I4-2+I1*60)+FP(I4)
231  1360  FS(I4-2+I1*60)=F1
232        FI(I2+40+I1*60)=FI(I2+38+I1*60)+S-FP(I2+40)
233  1500  X(I1)=X(I1)-DX(I1)
234        DO 1550 I5=60,N1,2
235        IF(FI(I5).GE.0.0)GOTO 1550
236        FI(I5)=0.0
237  1550  FT(I5)=FI(I5)
238        RETURN
239        END
240  C
241  C
242  C            COLD RECEPTOR FIRING RATE SUBROUTINE
243  C
244  C
245        SUBROUTINE COLD (Y,F)
246        DOUBLE PRECISION P0,P1,P2,P3,P4,P5,P6,P7,
247       &P8,P9,P10,Y,F
```

328

```
248          P0=-190053.1306D0
249          P1=85318.078D0
250          P2=-16974.919D0
251          P3=1972.4509D0
252          P4=-148.33377D0
253          P5=7.5486723D0
254          P6=-.263433230D0
255          P7=.0062289589D0
256          P8=-.000095563808D0
257          P9=-.0000008594993D0
258          P10=-.00000000034432887D0
259          F=P0 + Y*(P1+Y*(P2+Y*(P3+Y*(P4+Y*(P5+Y*(P6+
260     &Y*(P7+Y*(P8+Y*(P9+ P10*Y))))))))))
261          RETURN
262          END
263  C
264  C
265  C              WARM RECEPTOR FIRING RATE SUBROUTINE
266  C
267  C
268          SUBROUTINE WARM (Y,F)
269          DOUBLE PRECISION Q0,Q1,Q2,Q3,Q4,Q5,Q6,
270     &Q7,Q8,Q9,Q10,Y,F
271          Q0=.152664 7D05
272          Q1=-.5147704D04
273          Q2=.7707699D03
274          Q3=-.6747596D02
275          Q4=.3824428D01
276          Q5=-.1466418D00
277          Q6=.3852671D-02
278          Q7=-.6849608D-04
```

329

```
279    Q8=.7888965D-06
280    Q9=-.5317314D-08
281    Q10=.1593604D-10
282    F=Q0 + Y*(Q1+Y*(Q2+Y*(Q3+Y*(Q4+Y*(Q5+Y*(Q6+
283   &Y*(Q7+Y*(Q8+Y*(Q9+Y*Q10)))))))))
284    RETURN
285    END
```

II. Predicting the Relative Thermogenic Drive from the Generalized Neural Response to a Thermal Stimulus in Humans

```fortran
C
C
C     SUPERPOSITION OF METABOLIC RESPONSES TO THE
C     NEURAL CODED TEMPERATURE INFORMATION FROM
C     CORE AND CUTANEOUS THERMORECEPTORS.  THE
C     NEURAL CODED INFORMATION HAS PREVIOUSLY BEEN
C     DETERMINED WITH PROGRAM : NEURAL .
C
C
C
C          IGOR B. MEKJAVIC
C          S.F.U., 1983
C
C
C
C
C
      DIMENSION NC(6000),NR(6000),NE(6000),NT(6000),NW(6000),
     &M(200),MI(6000),MP(6000),MC(6000),MR(6000),ME(6000),MT(6000),
     &MW(6000),MF(6000),NCS(6000),NRS(6000),NES(6000),NTS(6000),
     &NWS(6000),MCS(6000),MRS(6000),MES(6000),MTS(6000),MWS(6000)
C
      REAL NC,NR,NE,NT,NW,M,MI,MP,MC,MR,ME,MT,MW,MF,
     &NCS,NRS,NES,NTS,NWS,MCS,MRS,MES,MTS,MWS
C
C
C
C     READ NEURAL DATA GENERATED BY PROGRAM MOD1
C
C
```

```
31        N=1
32    120 READ(1,180,END=200)NC(N),NR(N),NE(N),NT(N),NW(N),
34        &NCS(N),NRS(N),NES(N),NTS(N),NWS(N)
34.5  180 FORMAT(8X,10F10.3)
35        N=N+1
36        GOTO 120
37    200 N=N-1
38    C
39    C
40    C         READ METABOLIC RATE FROM RAW DATA FILE
41    C         UNIT = 2
42    C
43    C
44        N1=1
45    220 READ(2,280,END=300)M(N1)
46    280 FORMAT(F6.3)
47        N1=N1+1
48        GOTO 220
49    300 N1=N1-1
50    C
51    C
52    C         METABOLIC RESPONSE DUE TO SKIN COLD RECEPTION
53    C
54    C
55    350 CALL METAB (NC,MC,N,I4)
56    C
57    C
58    C         METABOLIC RESPONSE DUE TO RECTAL COLD RECEPTION
59    C
60    C
61    400 CALL METAB (NR,MR,N,I4)
```

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```
62    C
63    C
64    C
65    C       METABOLIC RESPONSE DUE TO ESOPHAGEAL COLD RECEPTION
66    C
67    450   CALL METAB (NE,ME,N,I4)
68    C
69    C       METABOLIC RESPONSE DUE TO TYMPANIC WARM RECEPTION
70    C
71    C
72    C
73    500   CALL METAB (NT,MT,N,I4)
74    C
75    C       METABOLIC RESPONSE DUE TO SKIN WARM RECEPTION
76    C
77    C
78    C
79    550   CALL METAB (NW,MW,N,I4)
80    C
81    C       METABOLIC RESPONSE DUE SKIN COLD RECEPTION
82    C       STATIC RESPONSE ONLY.
83    C
84    C
85    C
86    560   CALL METAB (NCS,MCS,N,I4)
87    C
88    C       METABOLIC RESPONSE DUE TO RECTAL COLD RECEPTION :
89    C       STATIC RESPONSE ONLY.
90    C
91    C
92    C
```

334

```
 93  565   CALL METAB (NRS,MRS,N,I4)
 94        C
 95        C
 96        C     METABOLIC RESPONSE DUE TO ESOPHAGEAL COLD RECEPTION :
 97        C     STATIC RESPONSE ONLY.
 98        C
 99        C
100  570   CALL METAB (NES,MES,N,I4)
101        C
102        C
103        C     METABOLIC RESPONSE DUE TYMPANIC WARM RECEPTION :
104        C     STATIC RESPONSE ONLY.
105        C
106        C
107  575   CALL METAB (NTS,MTS,N,I4)
108        C
109        C
110        C     METABOLIC RESPONSE DUE TO SKIN WARM RECEPTION :
111        C     STATIC RESPONSE ONLY.
112        C
113        C
114  580   CALL METAB (NWS,MWS,N,I4)
114.2      C
114.4      C
115        C     ESTABLISH OUTPUT FILE FOR METABOLIC RESPONSE
116        C     TIME INCREMENT = 20 SECONDS.
117        C     UNIT = 3
118        C
119        C
120        WRITE(3,600)(MC(I5),MR(I5),ME(I5),MT(I5),MW(I5),
121       &MCS(I5),MRS(I5),MES(I5),MTS(I5),MWS(I5),I5=60,I4,20)
122  600   FORMAT(10F7.2)
123        C
```

```
124 C     ESTABLISH OUTPUT FILE CONTAINING THE CALCULATED
125 C     RELATIVE METABOLIC RESPONSE TO THE HYPOTHETICAL
126 C     NEURAL INFORMATION AND THE OBSERVED METABOLIC
127 C     RESPONSE. THIS FILE WILL ALLOW FOR FURTHER
128 C     ANALYSIS WITH BMDP-STATISTICAL PACKAGE.
129 C
130 C     TIME INCREMENT = 60 SECONDS
131 C     UNIT = 4
132 C
133 C
134 C
135       WRITE(4,700)(M(I6/60),MC(I6),MR(I6),ME(I6),MT(I6),MW(I6),
136      &MCS(I6),MRS(I6),MES(I6),MTS(I6),MWS(I6),I6=60,I4,60)
137 700   FORMAT(11F7.2)
138       STOP
139       END
140 C
141 C
142 C                    SUBROUTINE METABOLIC
143 C
144 C
145 C
146 C
147       SUBROUTINE METAB (X,MI,N,I4)
148       DIMENSION X(12000),MI(12000),MF(12000),MP(300),
149      &DX(12000)
150       REAL MI,MF,MP
151       N2=N-10
152       DO 1000 I=60,300,20
153 1000  MI(I)=0.0
154       DO 1020 I1=1,N2,10
```

```
155      DX(I1)= X(I1+10) - X(I1)
156      X1=-20.0
157      DO 1010 I2= 20,260,20
158      X1= X1 + 20.0
159      MP(I2) = DX(I1)*(1.0-EXP(-X1/30.))
160 1010 MI(I2-20+(I1-1)*2+60)=MI(I2-20+(I1-1)*2+60)+MP(I2)
161 1020 MI(I2+(I1-1)*2+60)=MI(I2-20+(I1-1)*2+60)+DX(I1)-MP(I2)
162      J=78+2*N2
163      DO 1030 I4=60,J,20
164 1030 MF(I4)=MI(I4)
165      RETURN
166      END
```

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APPENDIX VI. : Empirical Data

The emprical data presented in this section was collected during the cold water immersion and rewarming trials, as outlined in section D. The data was used to evaluate the metabolic response of humans to immersion in water at different temperatures and to rewarming, with and without the donation of heat to the respiratory tract. In section E, this data was used to develop and evaluate the time-dependent thermoregulatory model based on the theory of superposition.

Each graph is represented with a nomenclature, describing the experimental condition. The first two letters of the mnemonic represent the subject's initials (either AL, BC, DS, DT or RH). The proceeding two numbers specify the temperature of the immersion bath (either 10^m, 15^m or 20^m C), while the last letter refers to the nature of the inhalate; N for experiments where normal room temperature air was the inhalate and W where warm air (40^m-45^m C) saturated with water vapour was the inhalate.

The empirical data is presented in two sections. The first section consists of weigthed mean skin (according to the formula of Ramanathan, 1964) and core (rectal, esophageal and tympanic) temperature, as well as metabolic rate (in units of $ml.O_2/kg./min.$), during cooling and rewarming.

The second section consists of the cardiovascular responses (heart rate in beats/min.), during the immersion trials and rewarming procedure.

I. Average Skin and Core Temperatures, and Metabolic Rate during Cooling and Rewarming

Core temperature measurements were taken at rectal (closed circles), esophageal (crosses) and tympanic (open triangles) sites. Although measurements were recorded for each minute of cooling and rewarming, for reasons of clarity, only every second minute is plotted on the graphs.

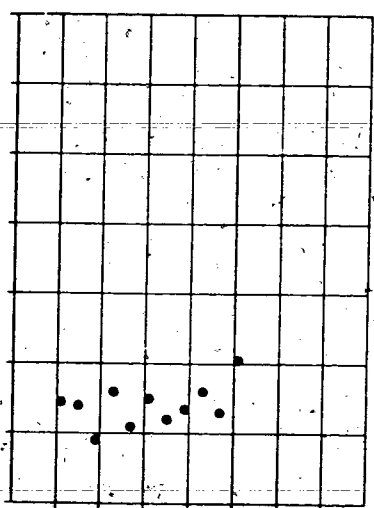Fig. A6.1 : Subject AL

    a) AL10N

    b) AL15N

    c) AL20N

    d) AL10W

    e) AL15W

    f) AL20W

341a

341b

Mean skin temp. (°C)

Core temp. (°C)

$\dot{V}O_2$ (ml./kg./min.)

Cooling time (min.)

Rewarming time (min.)

341c

Mean skin temp. (°C) / Core temp. (°C) / $\dot{V}O_2$ (ml./kg./min.) plotted against Cooling time (min.) and Rewarming time (min.)

341e

Mean skin temp. (°C)

Core temp. (°C)

$\dot{V}O_2$ (ml./kg./min.)

Cooling time (min.)

Rewarming time (min.)

341f
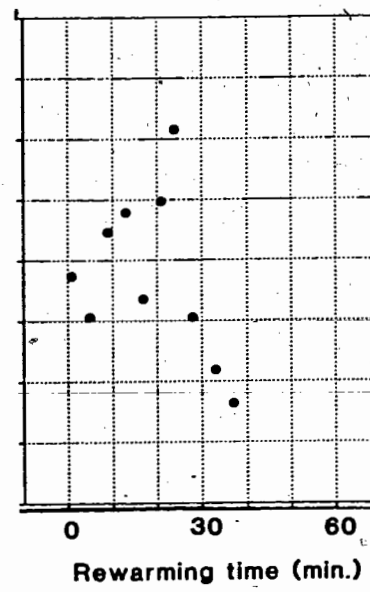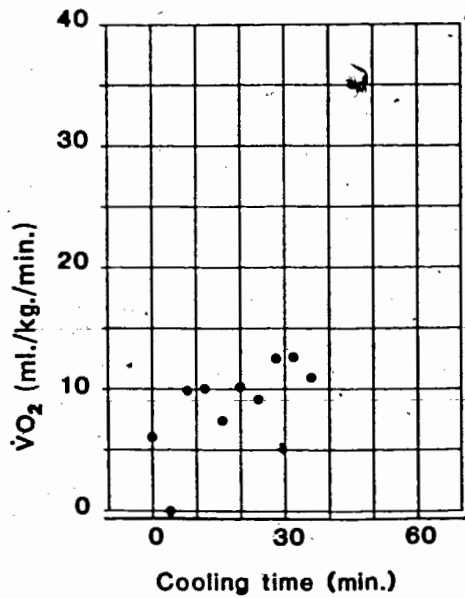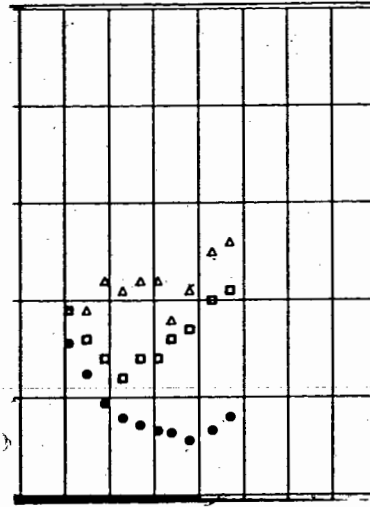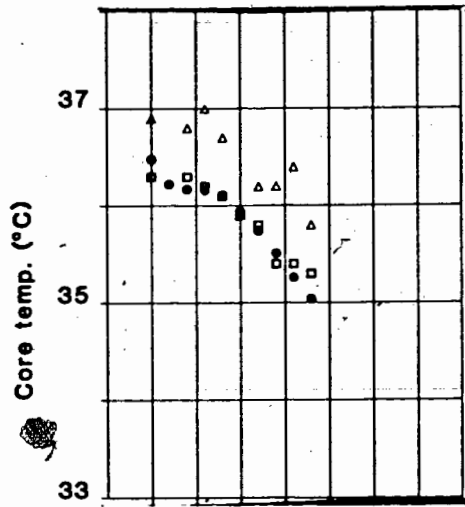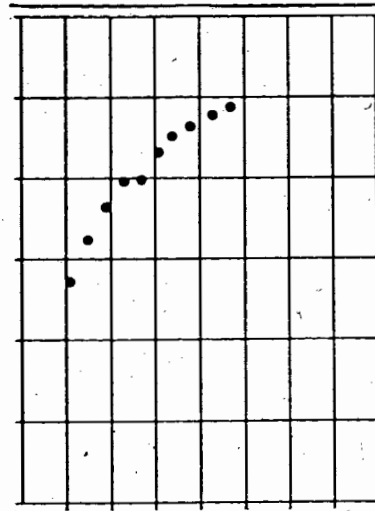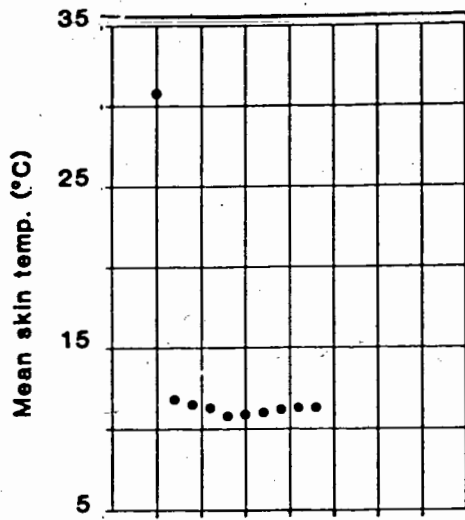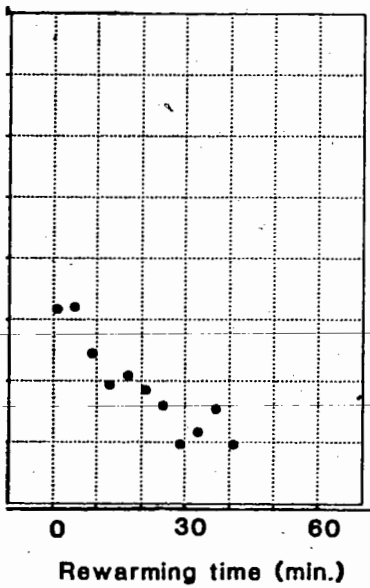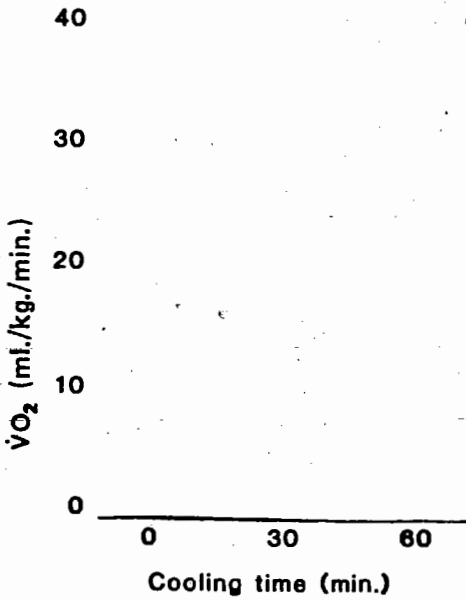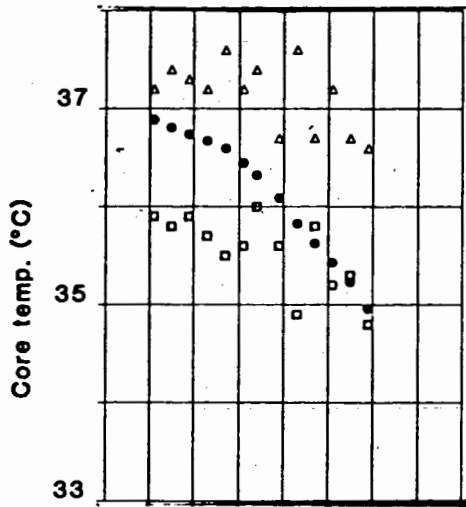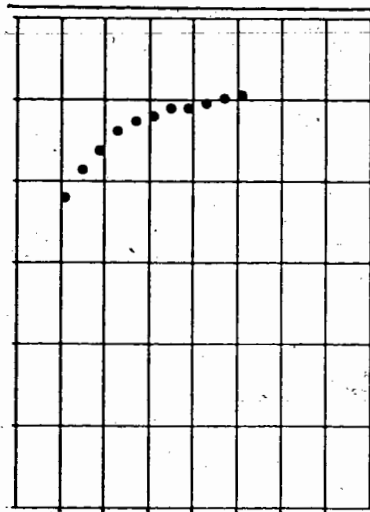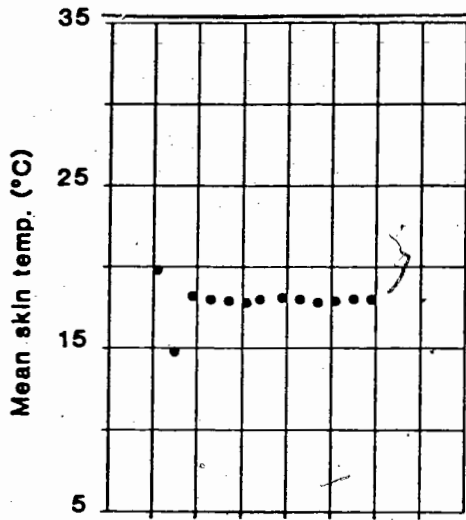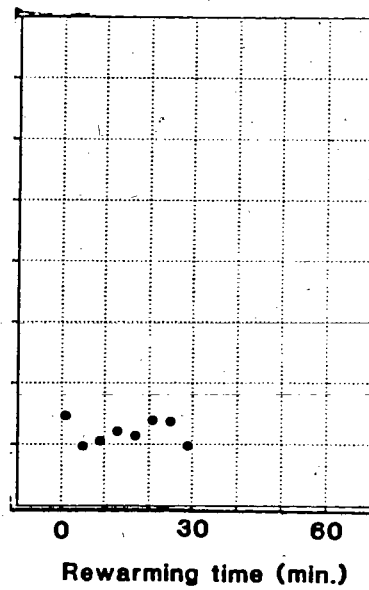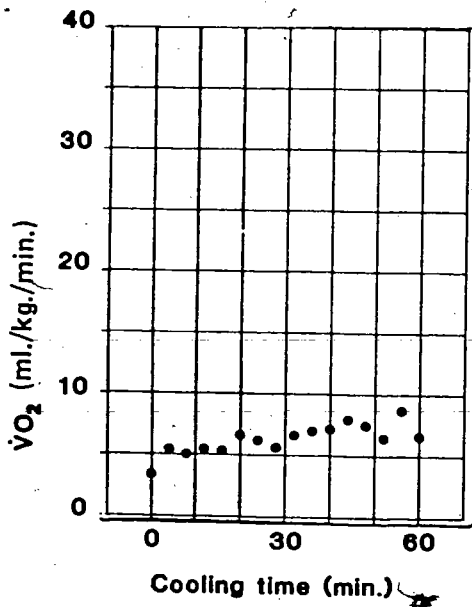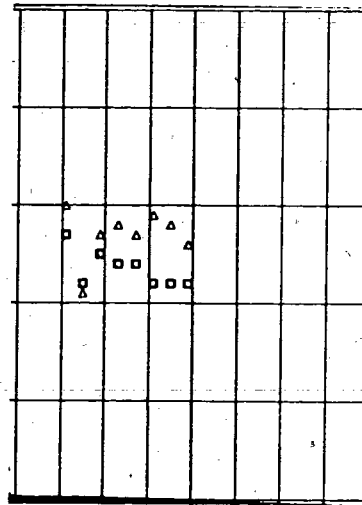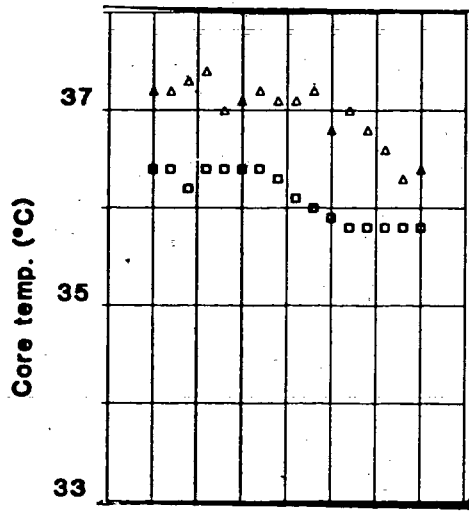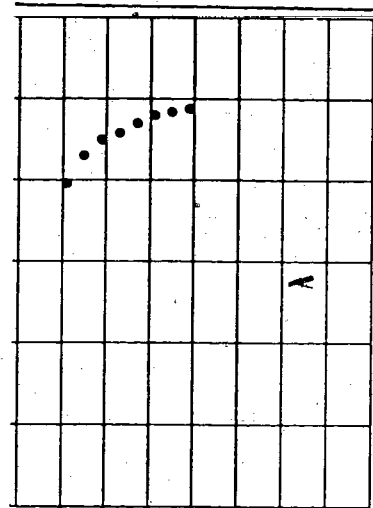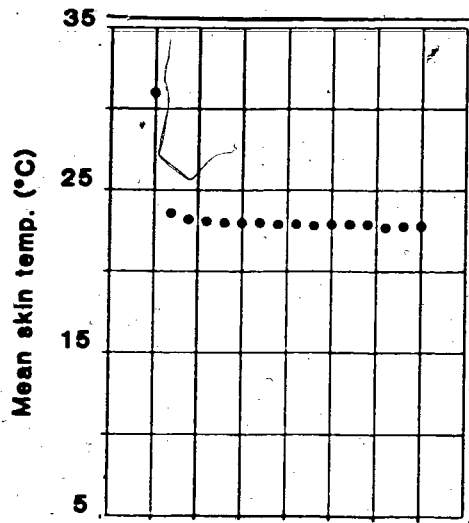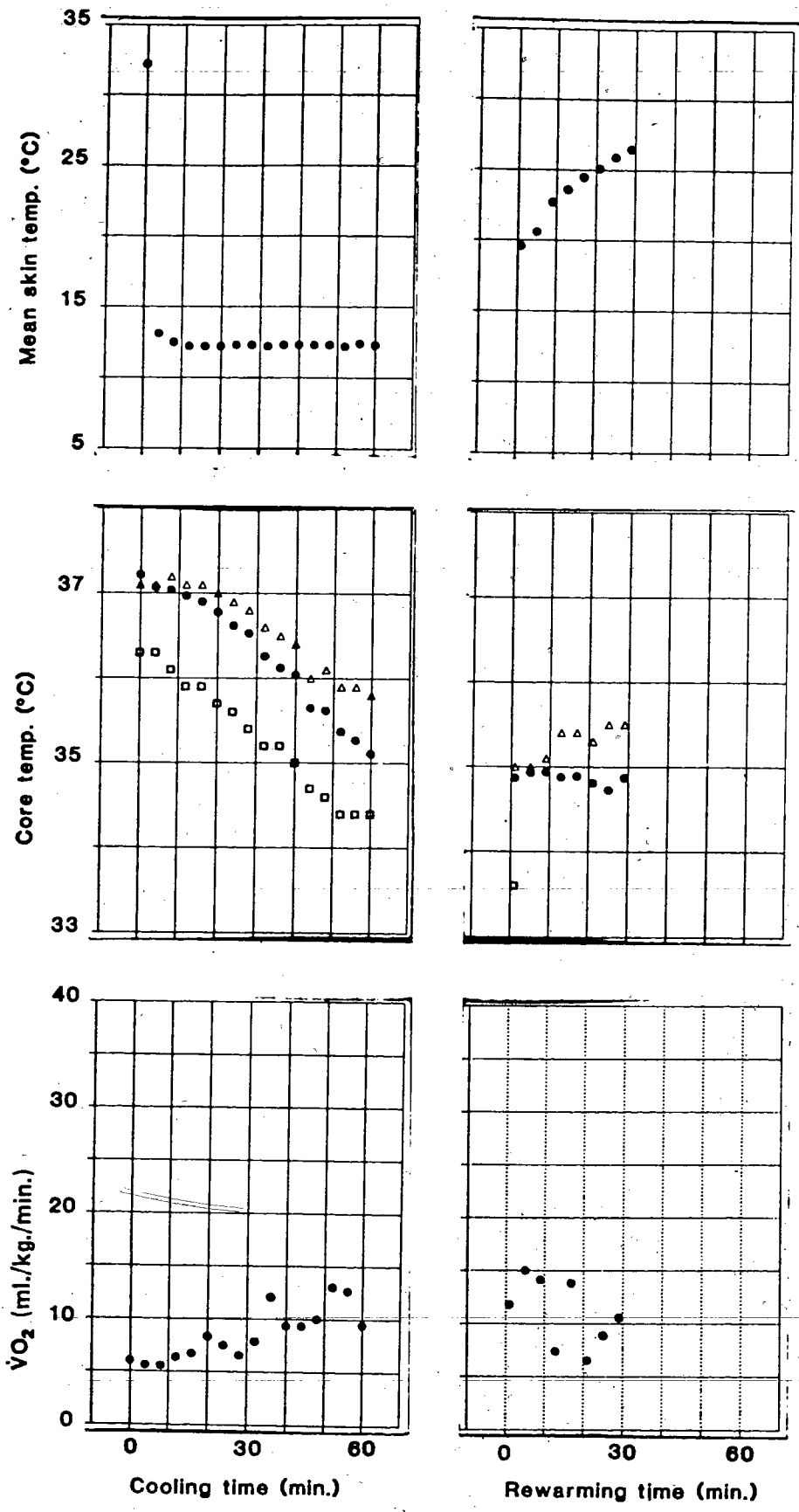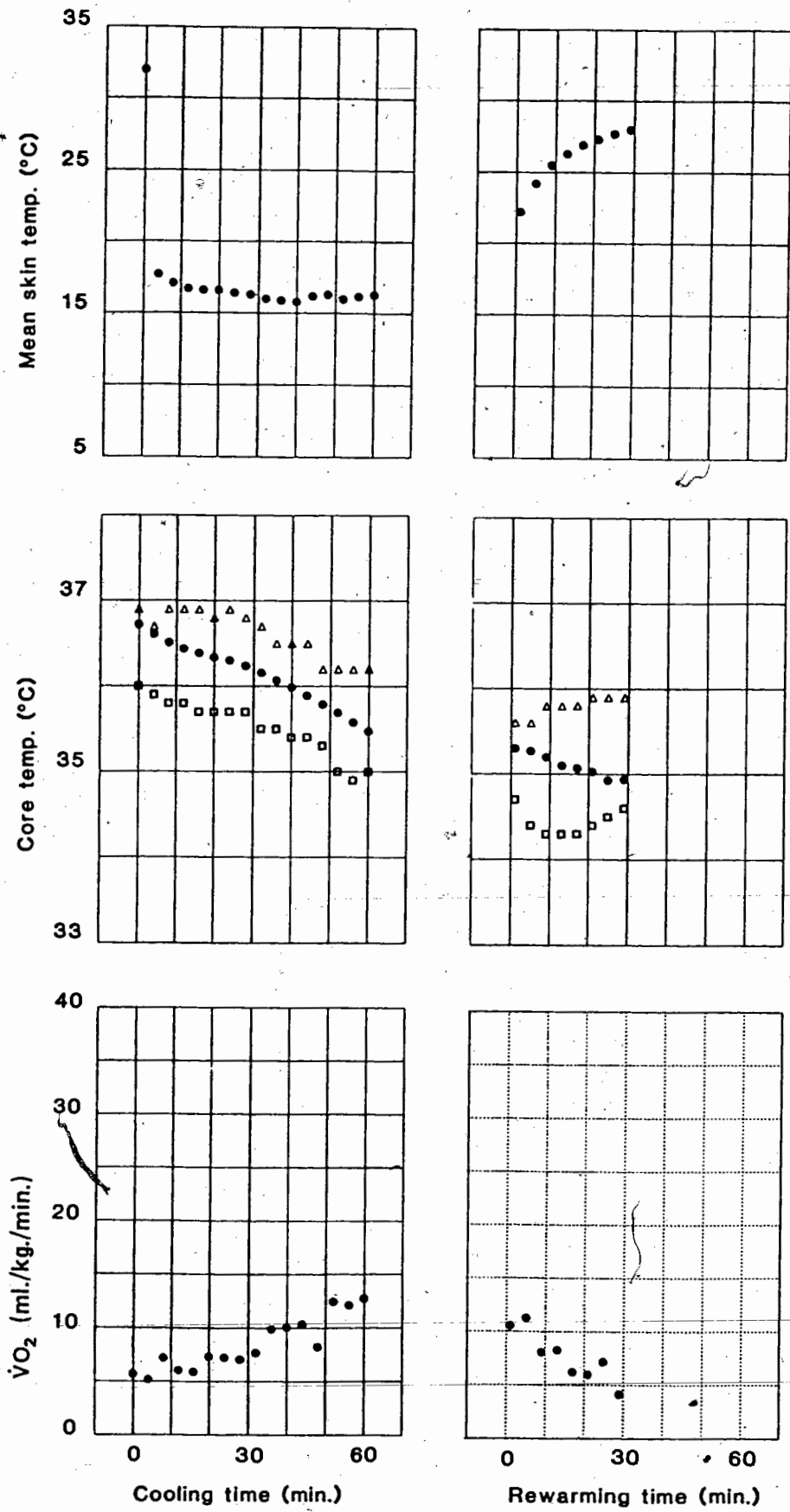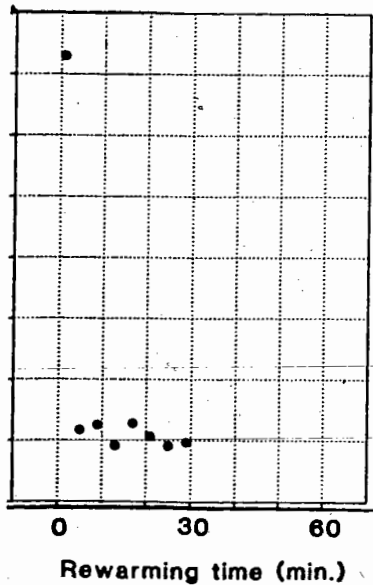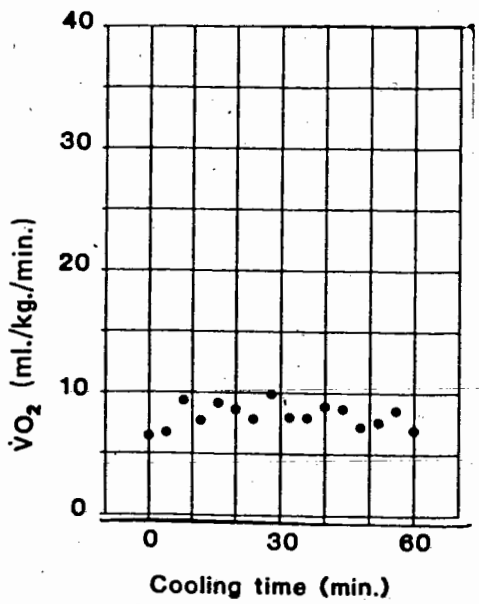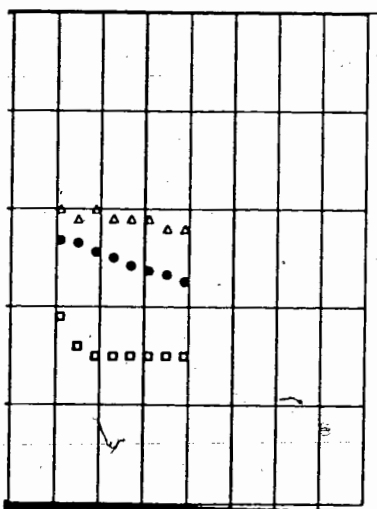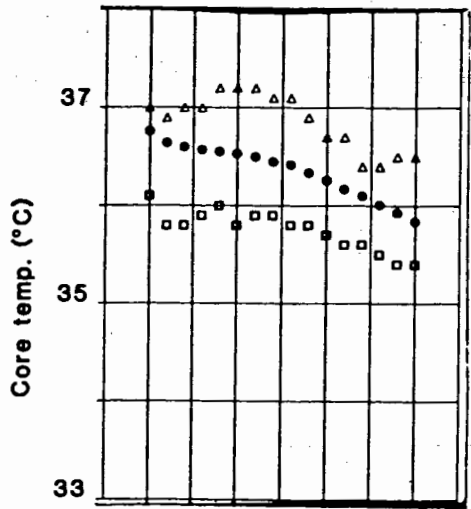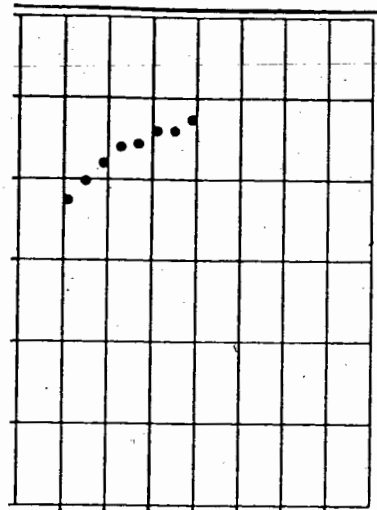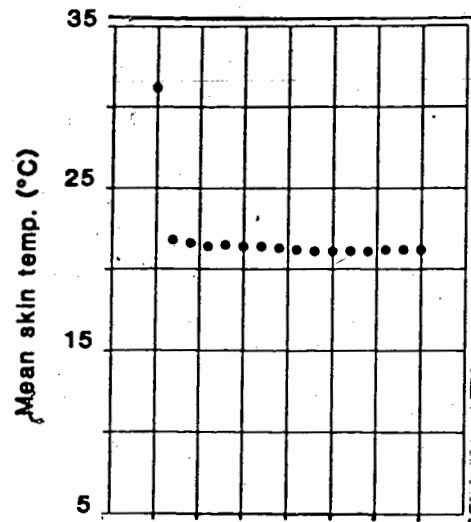
Fig. A6.2 : Subject BC

    a) BC10N

    b) BC15N

    c) BC20N

    d) BC10W

    e) BC15W

    f) BC20W

342a

342b

342d

342e

342f
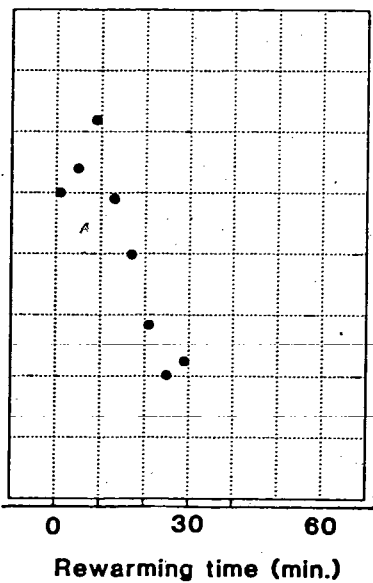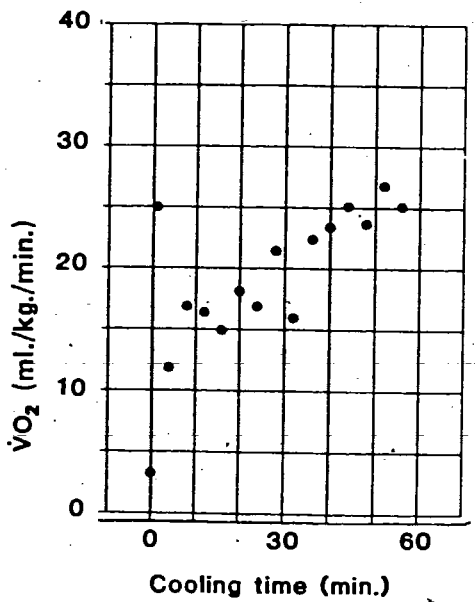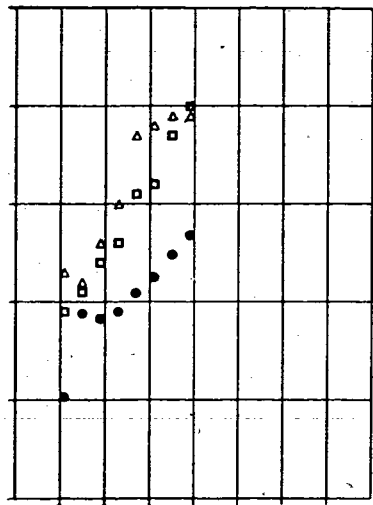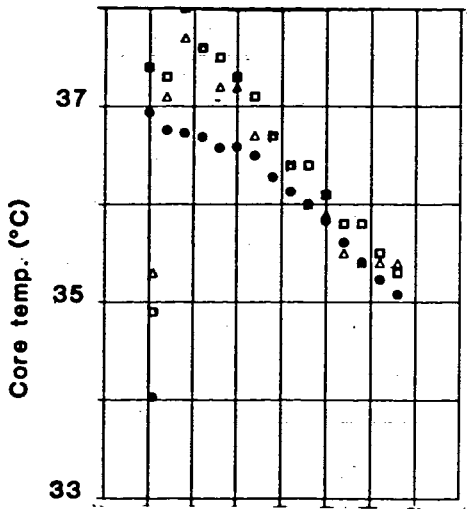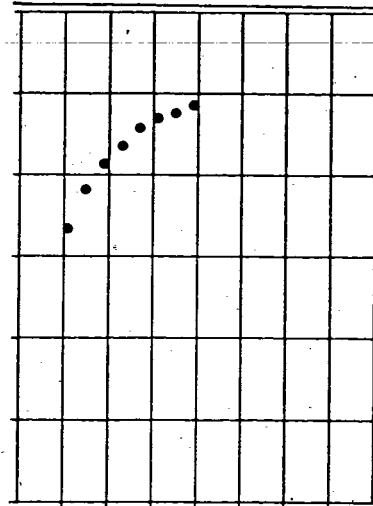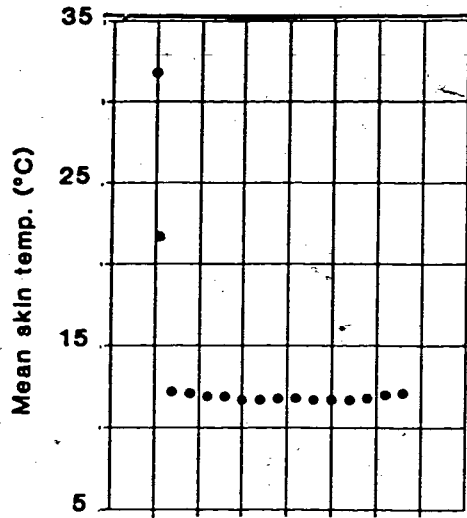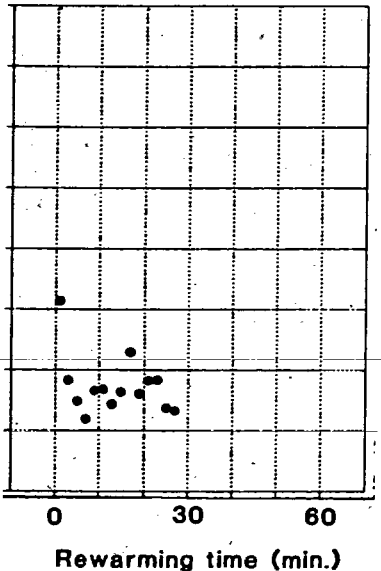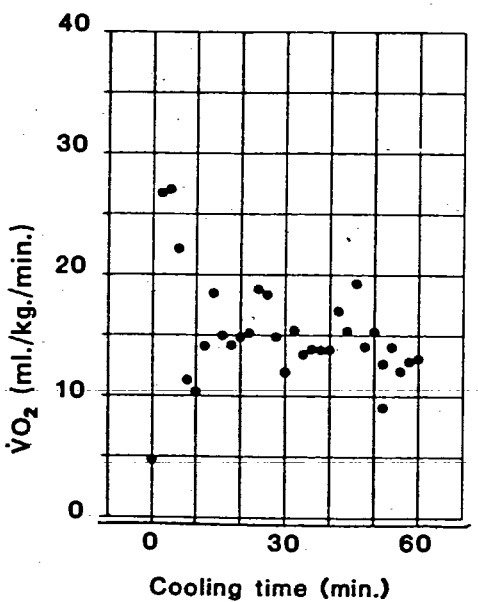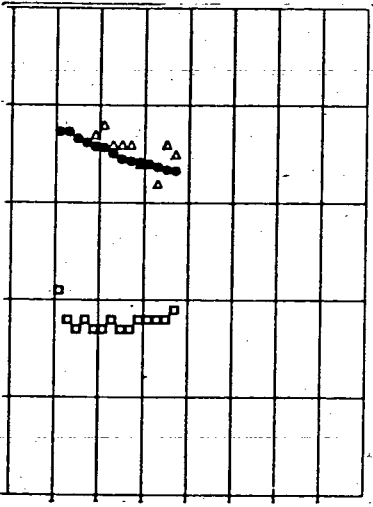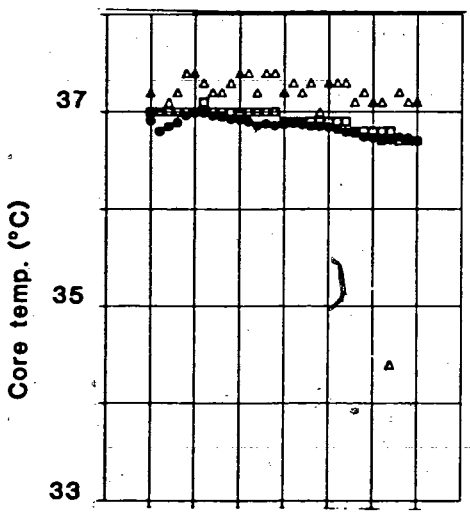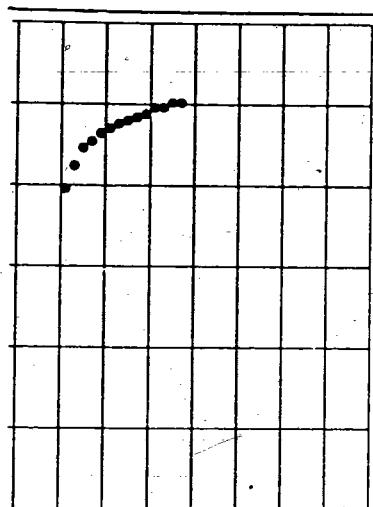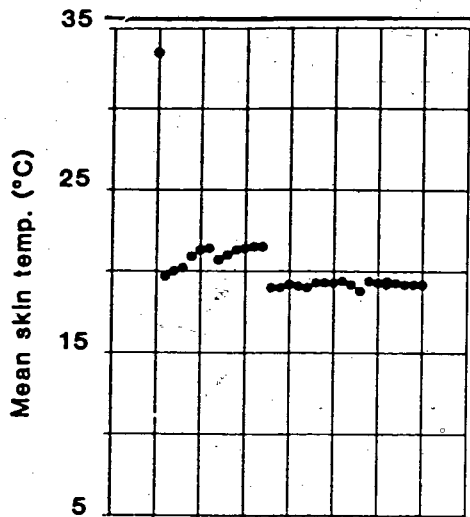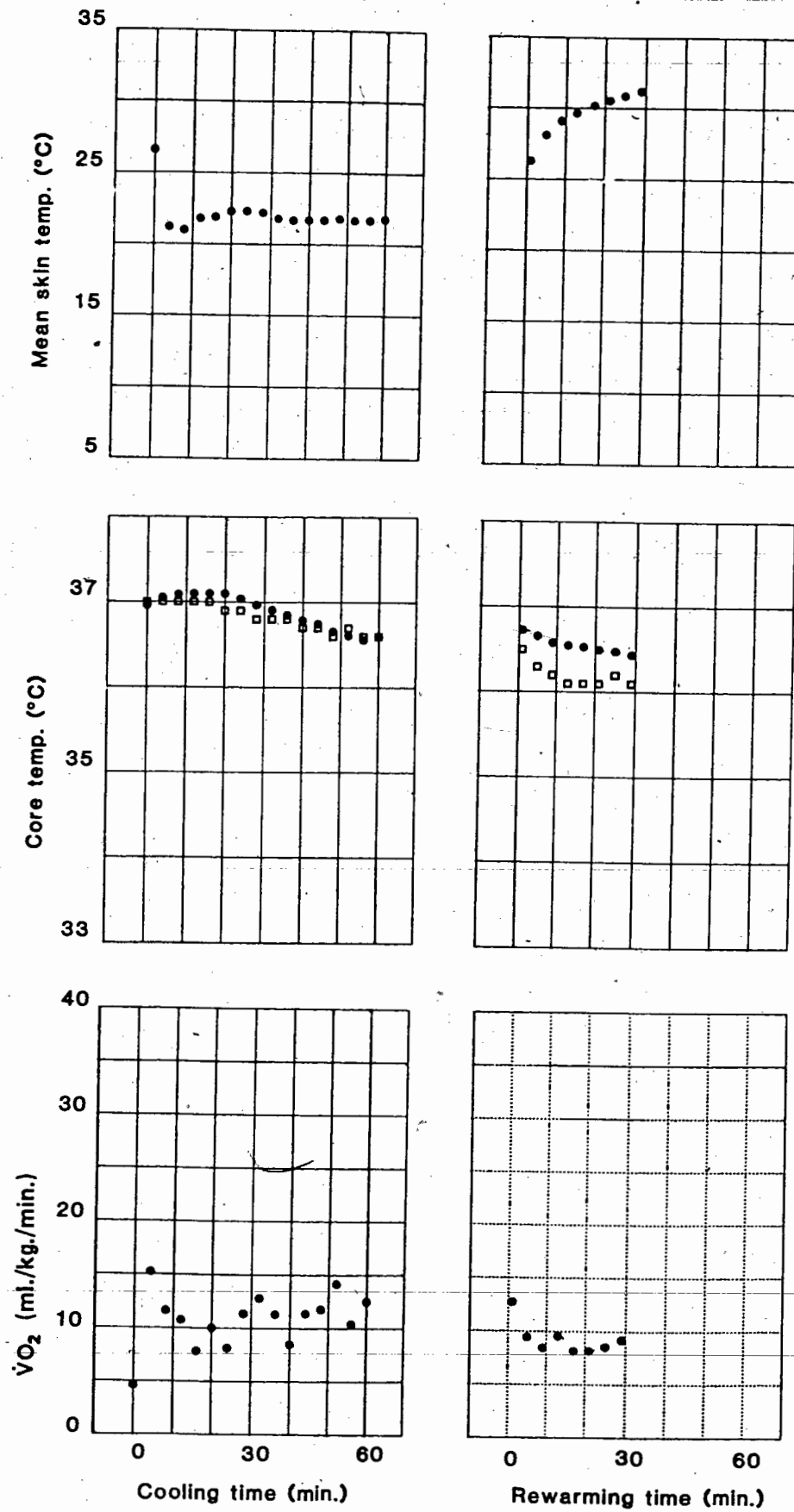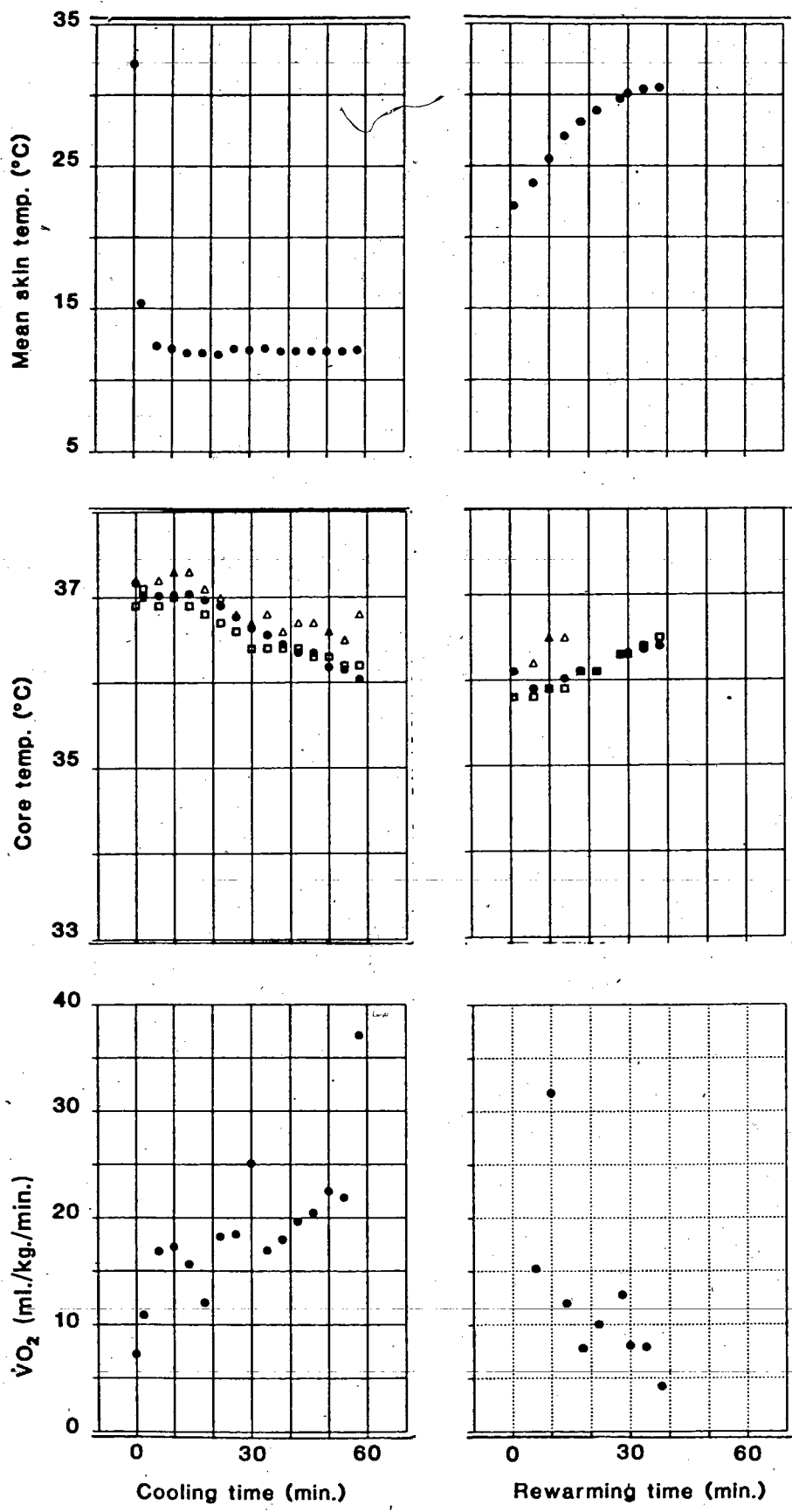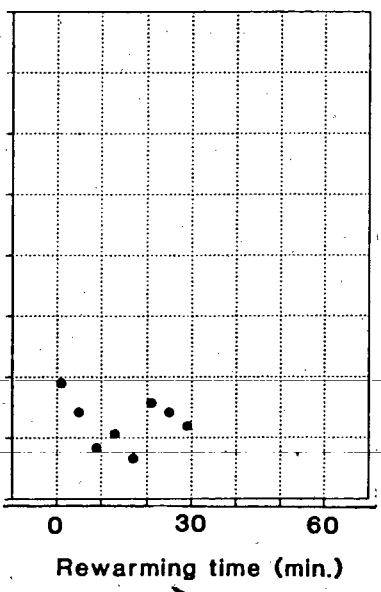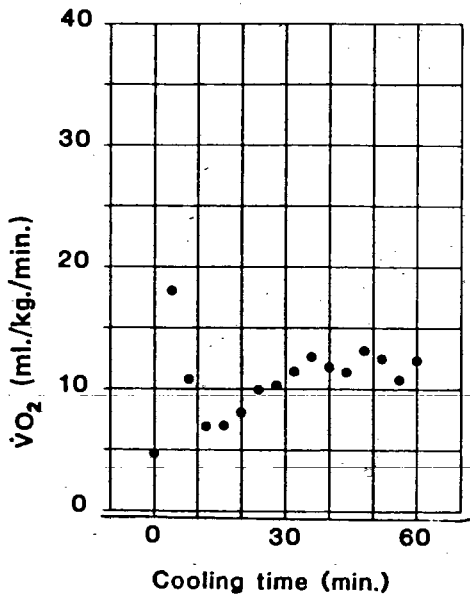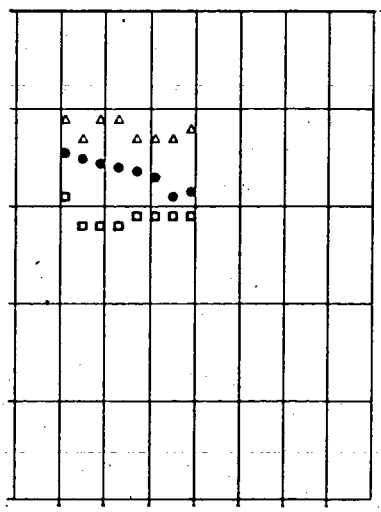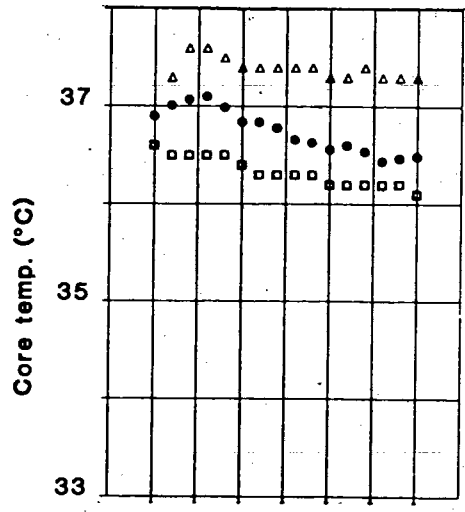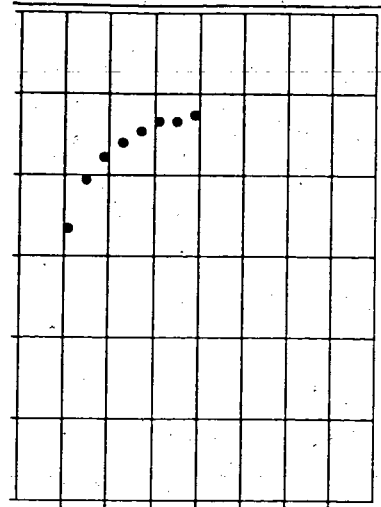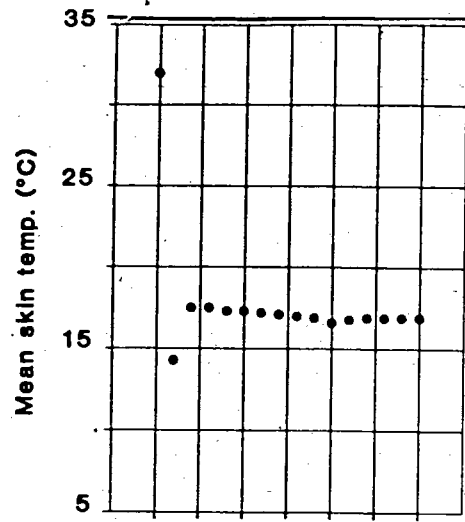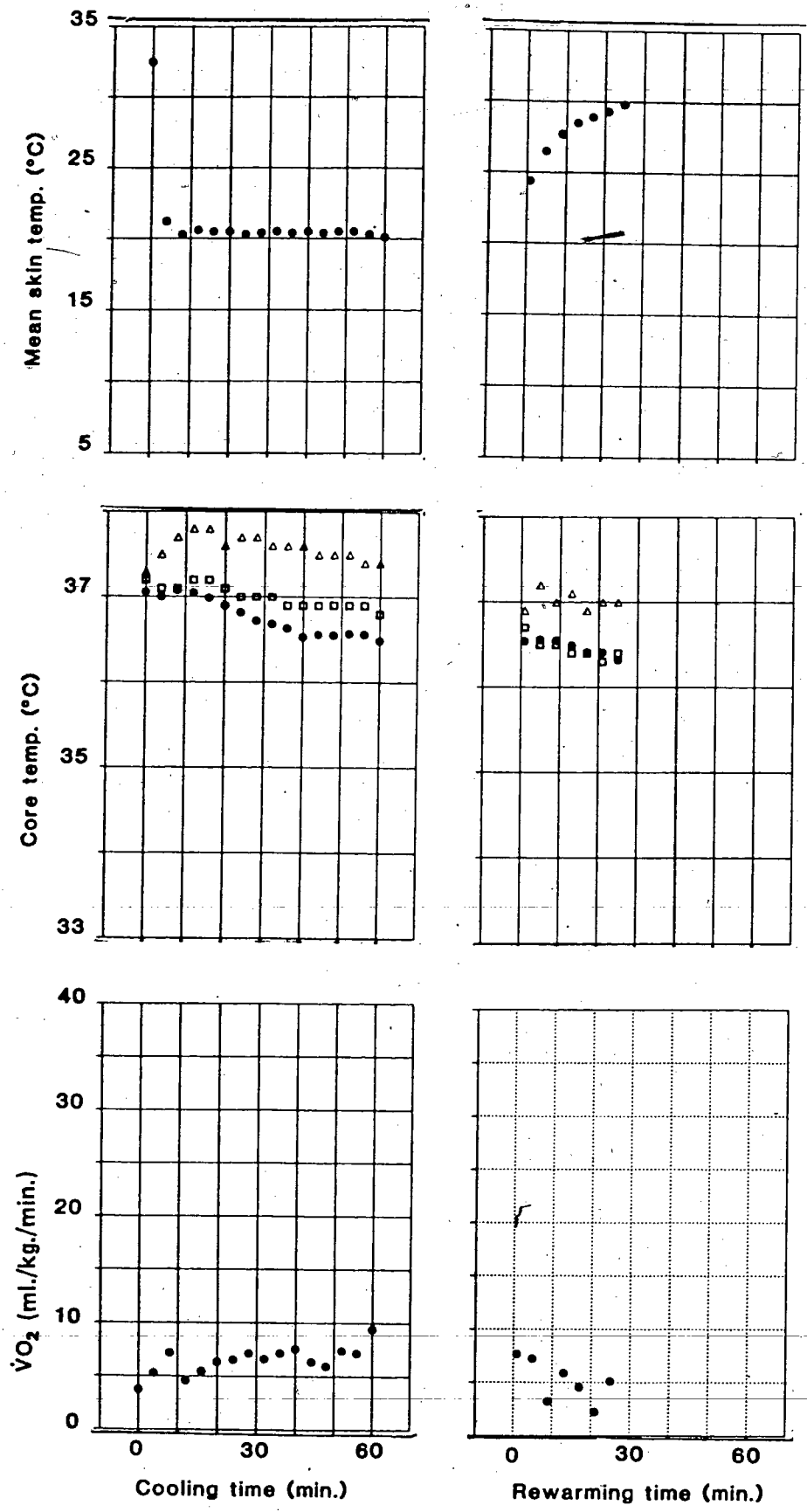
Fig. A6.3 : Subject DS

    a) DS10N

    b) DS15N

    c) DS20N

    d) DS10W

    e) DS15W

    f) DS20W

Mean skin temp. (°C)
Core temp. (°C)
$\dot{V}O_2$ (ml./kg./min.)

Cooling time (min.)
Rewarming time (min.)

343c

343d

Mean skin temp. (°C)

Core temp. (°C)

$\dot{V}O_2$ (ml./kg./min.)

Cooling time (min.)

Rewarming time (min.)

343f
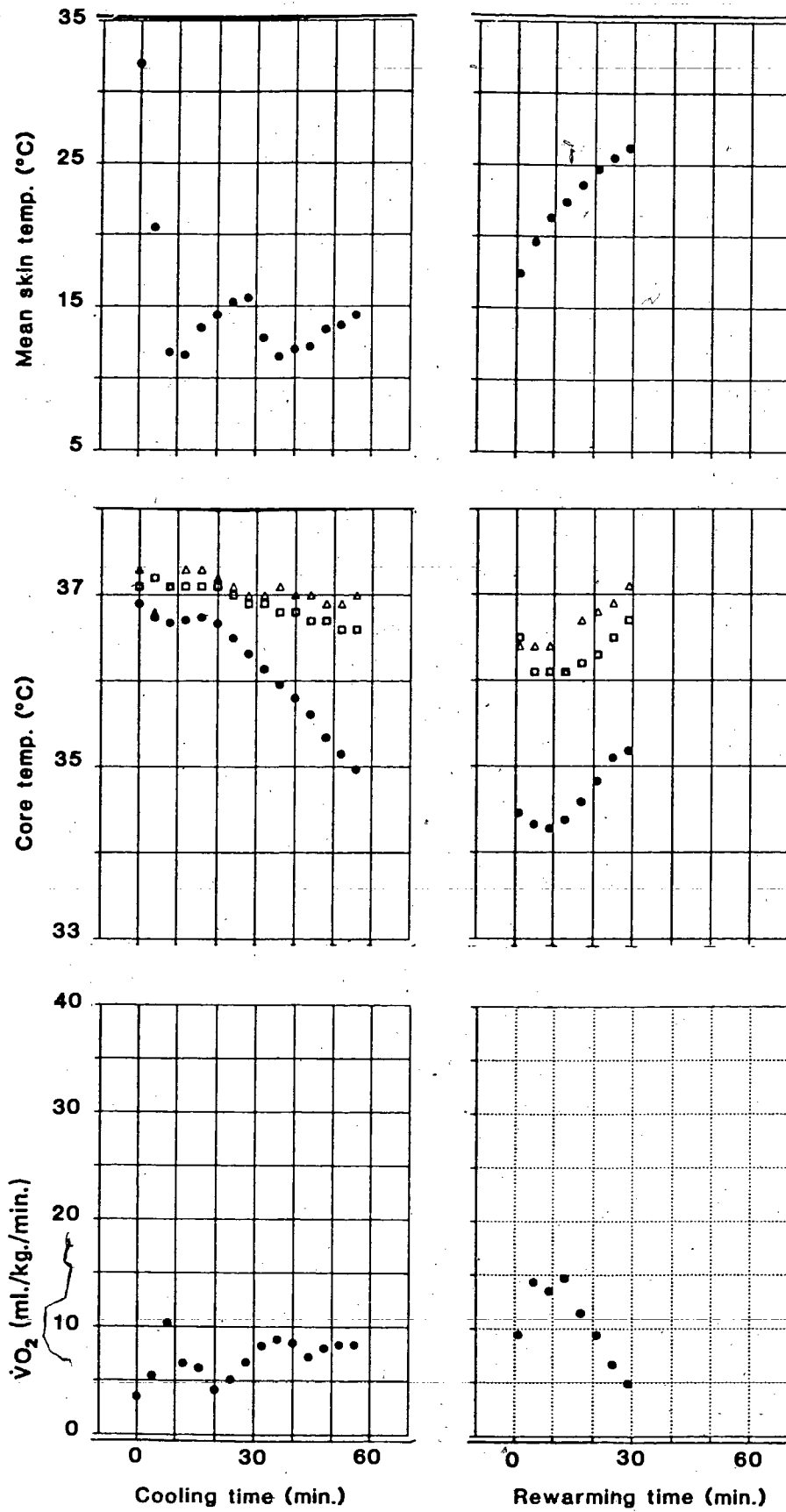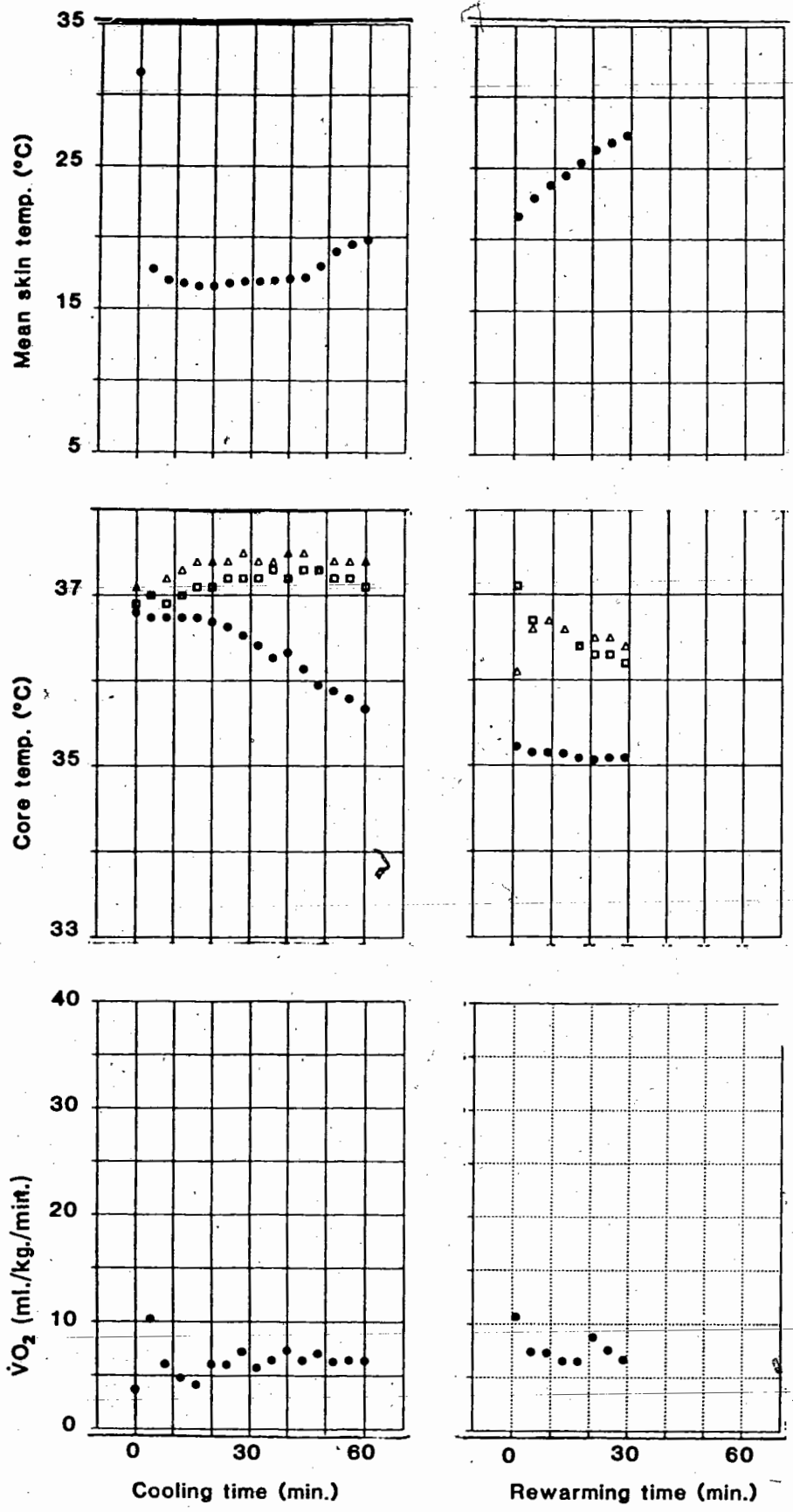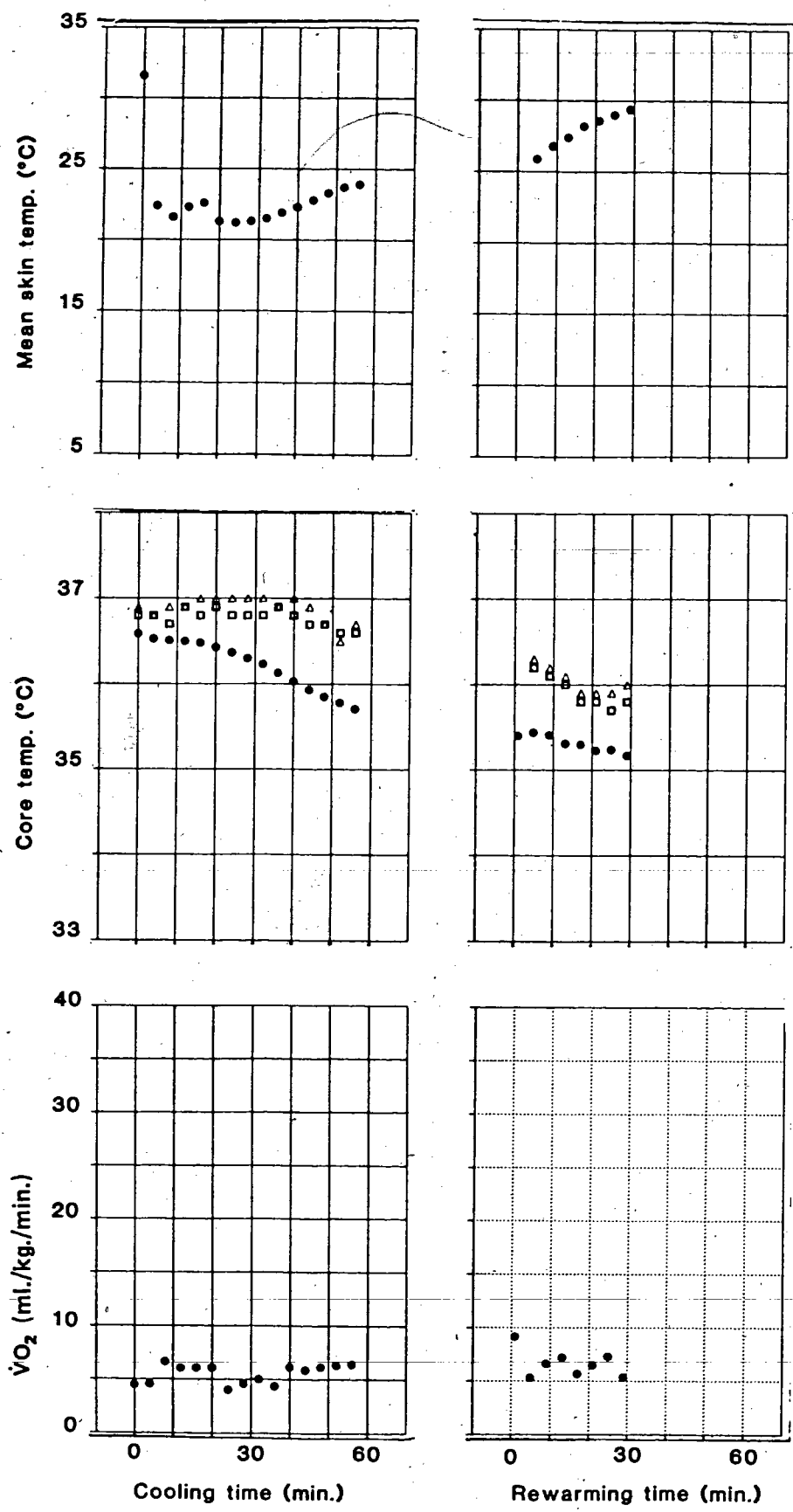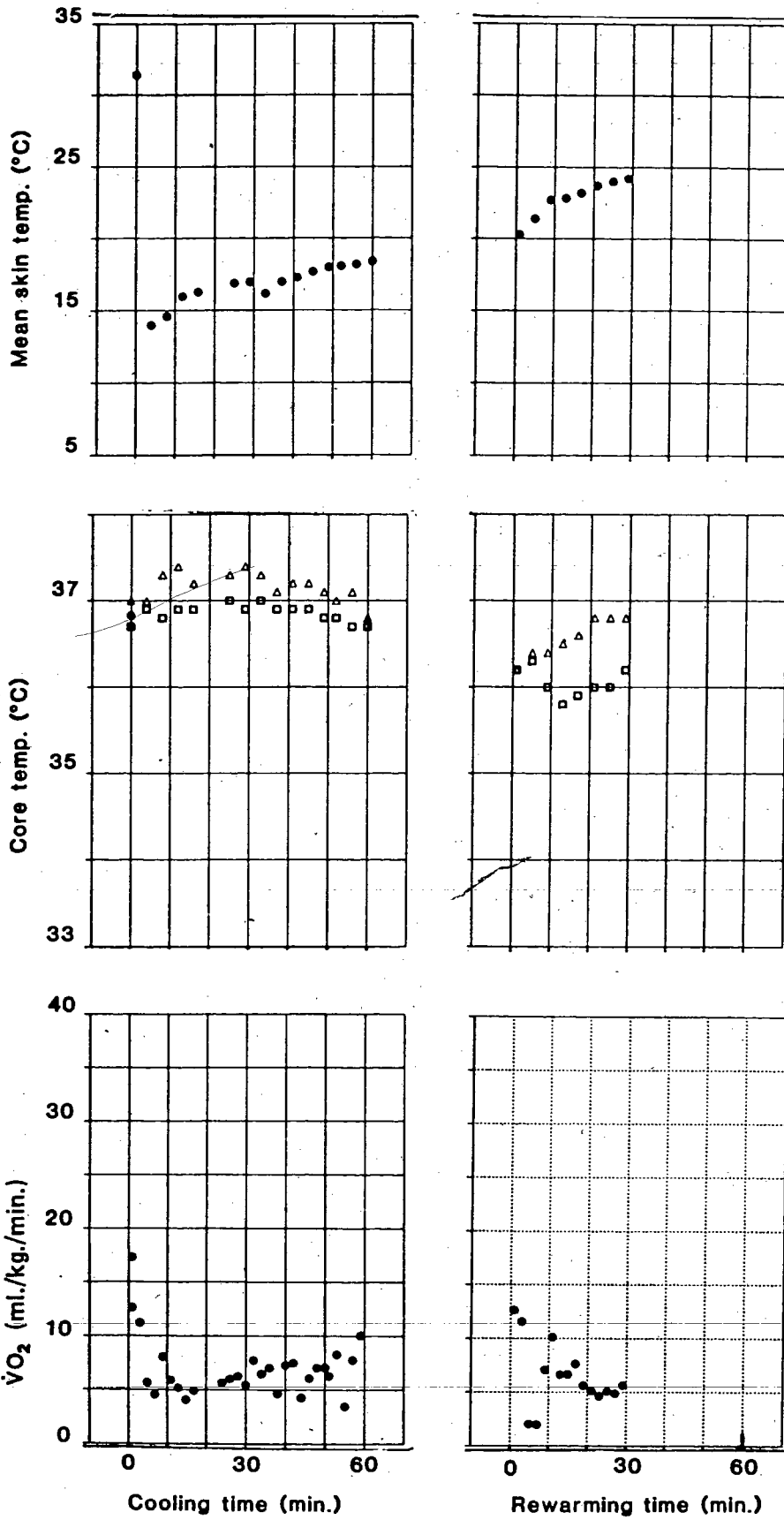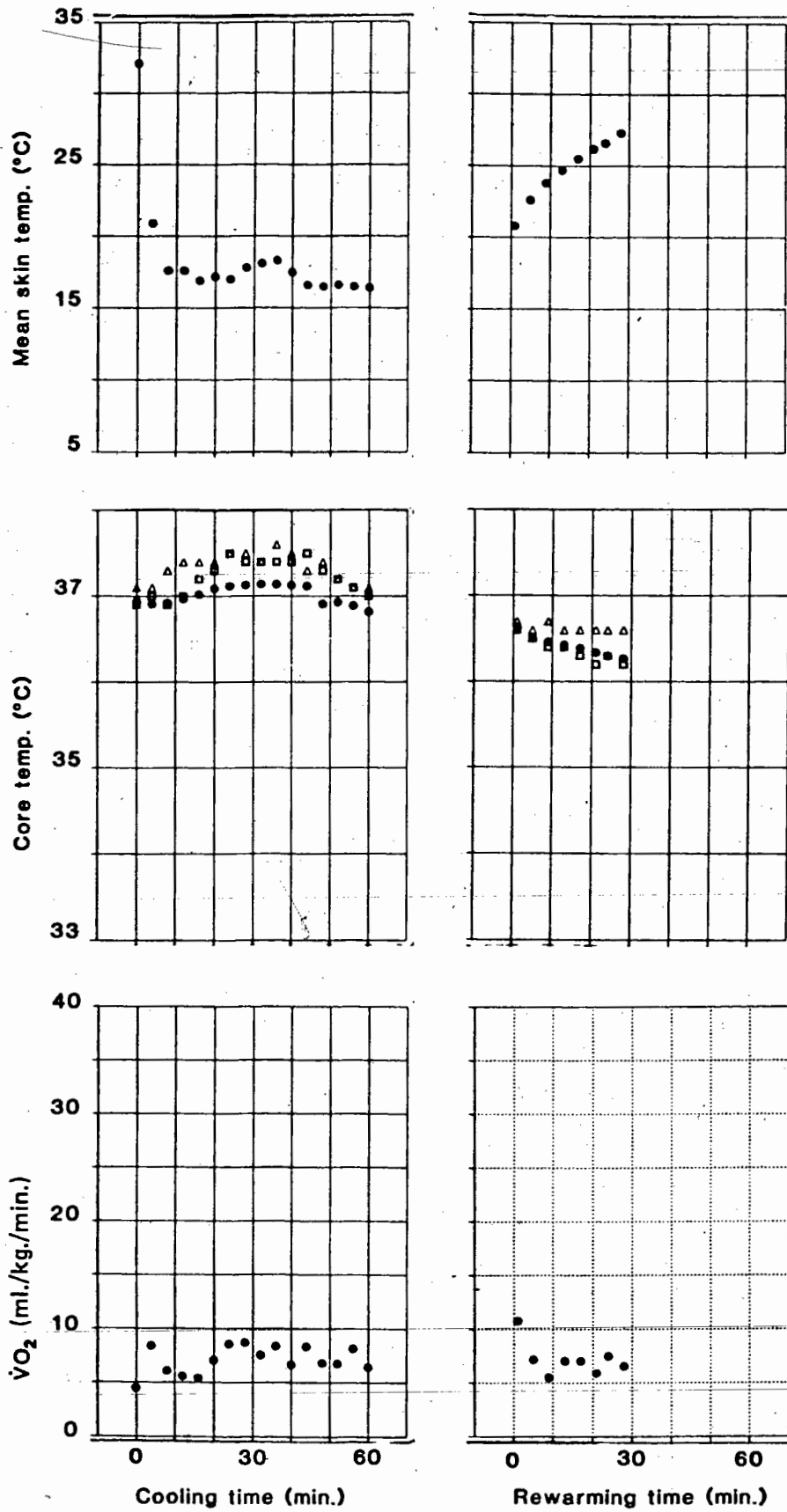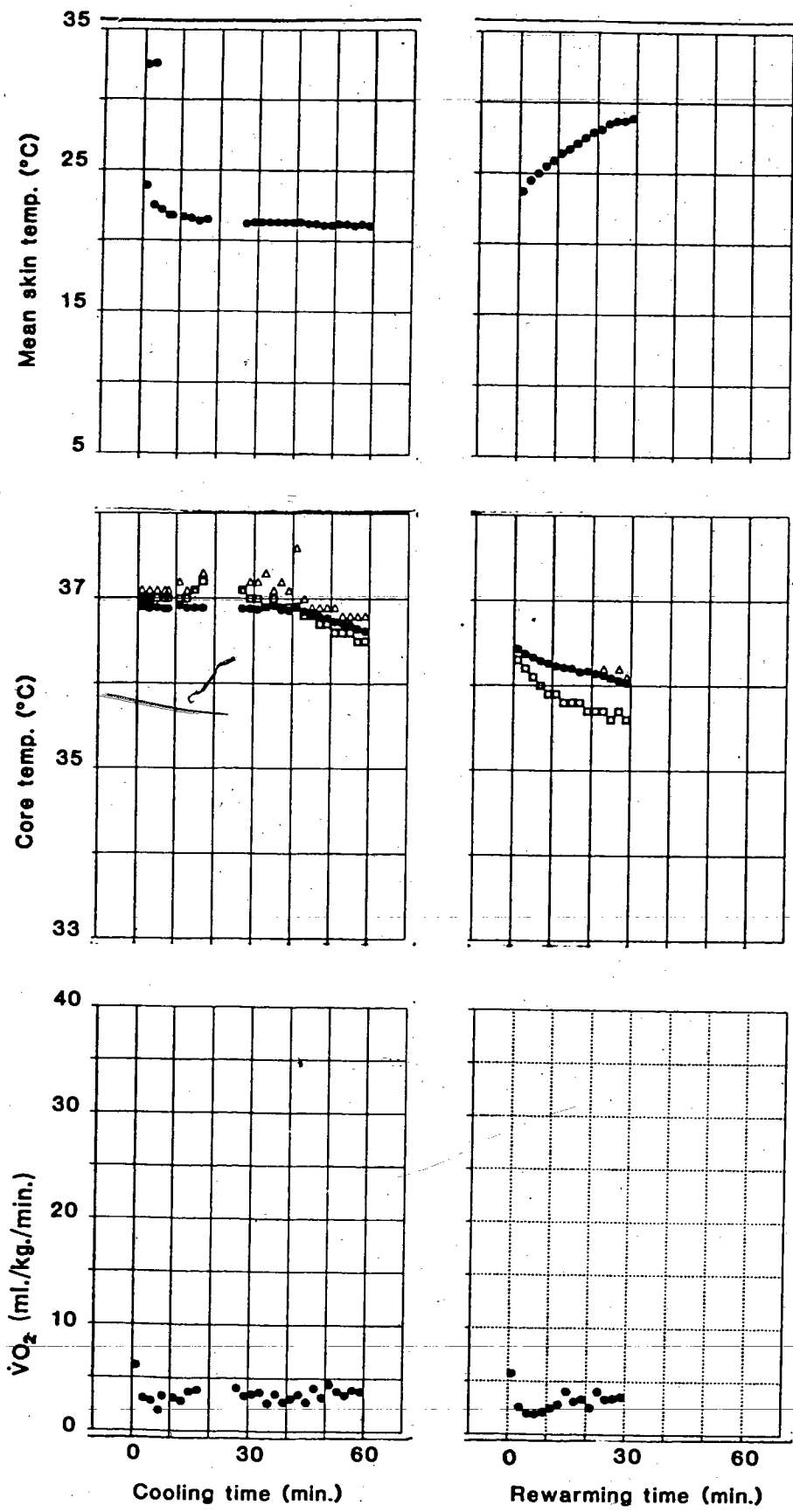
Fig. A6.4 : Subject DT

   a) DT10N

   b) DT15N

   c) DT20N

   d) DT10W

   e) DT15W

   f) DT20W

344a

344b

344c

344d

Mean skin temp. (°C)

Core temp. (°C)

V̇O₂ (ml./kg./min.)

Cooling time (min.)

Rewarming time (min.)

344e
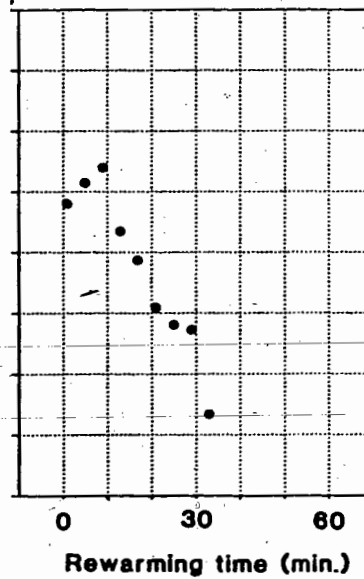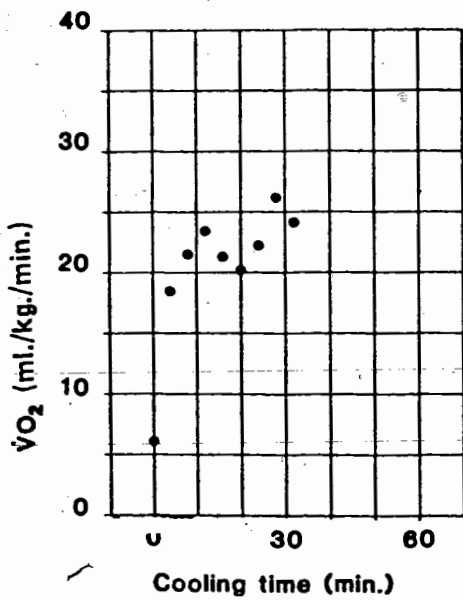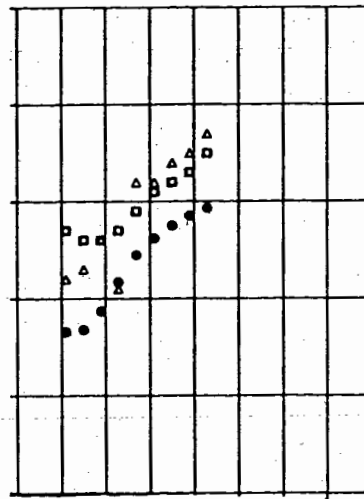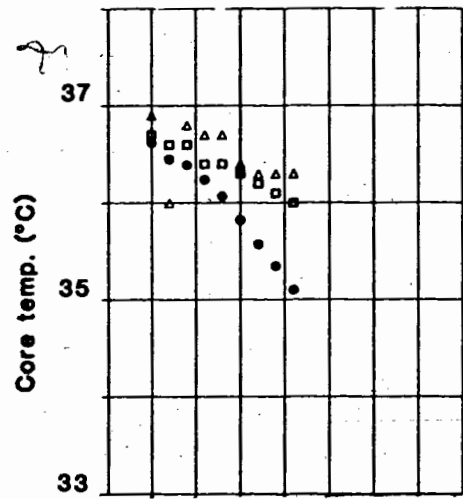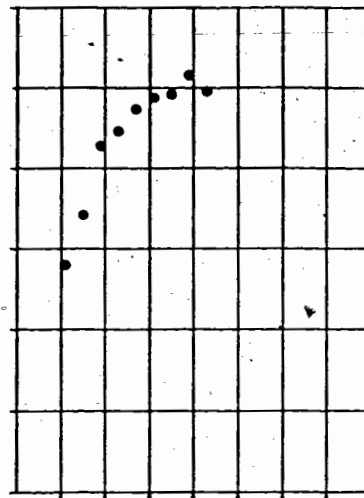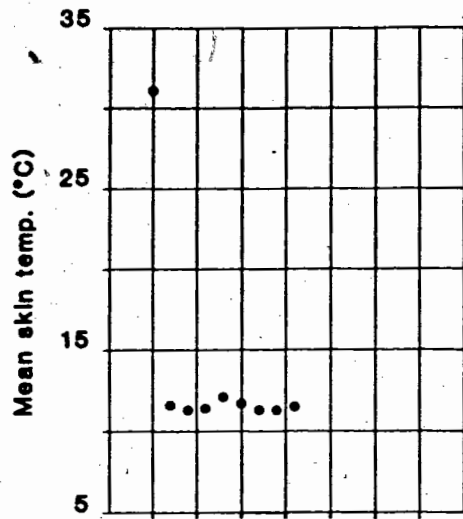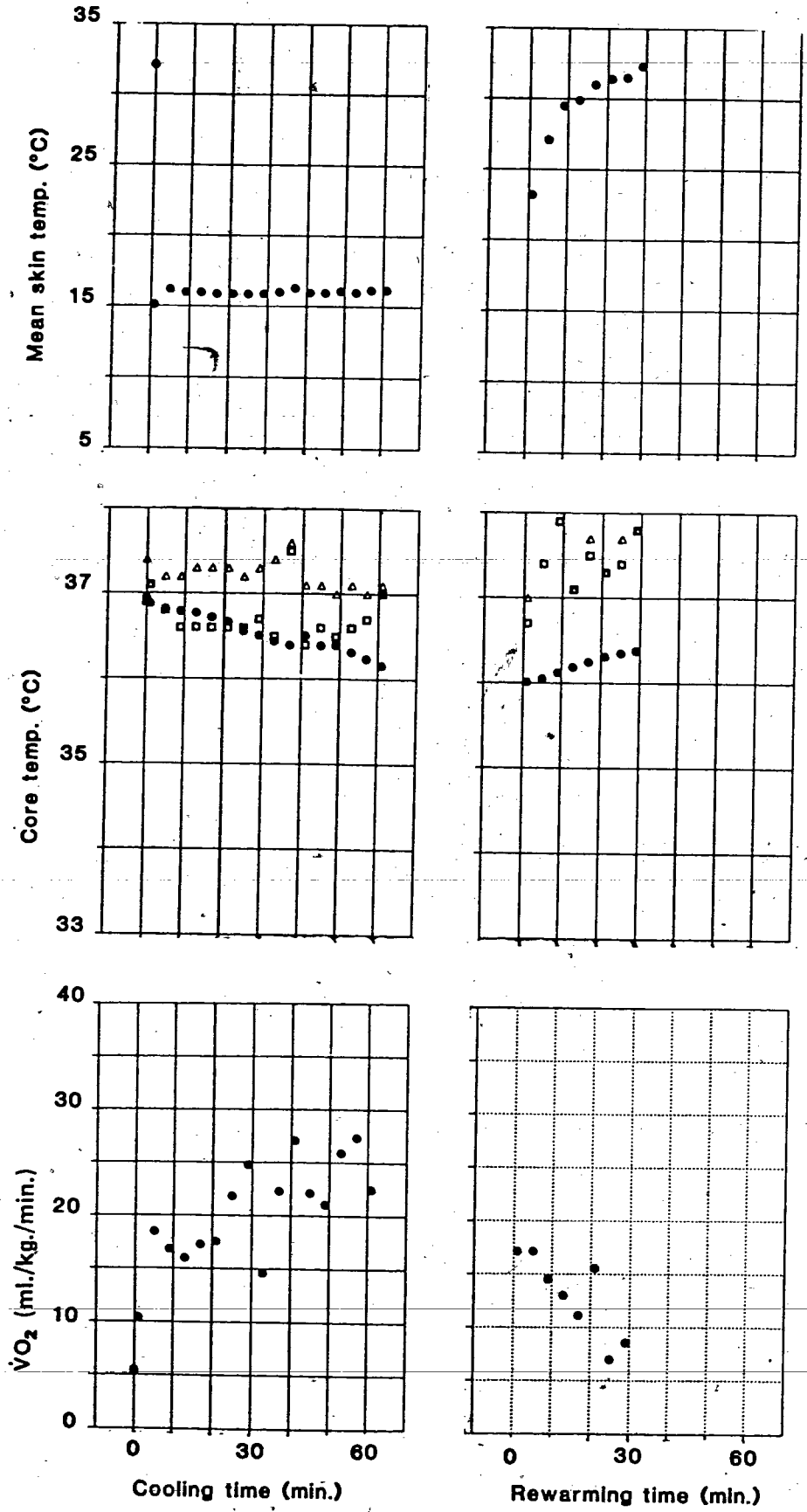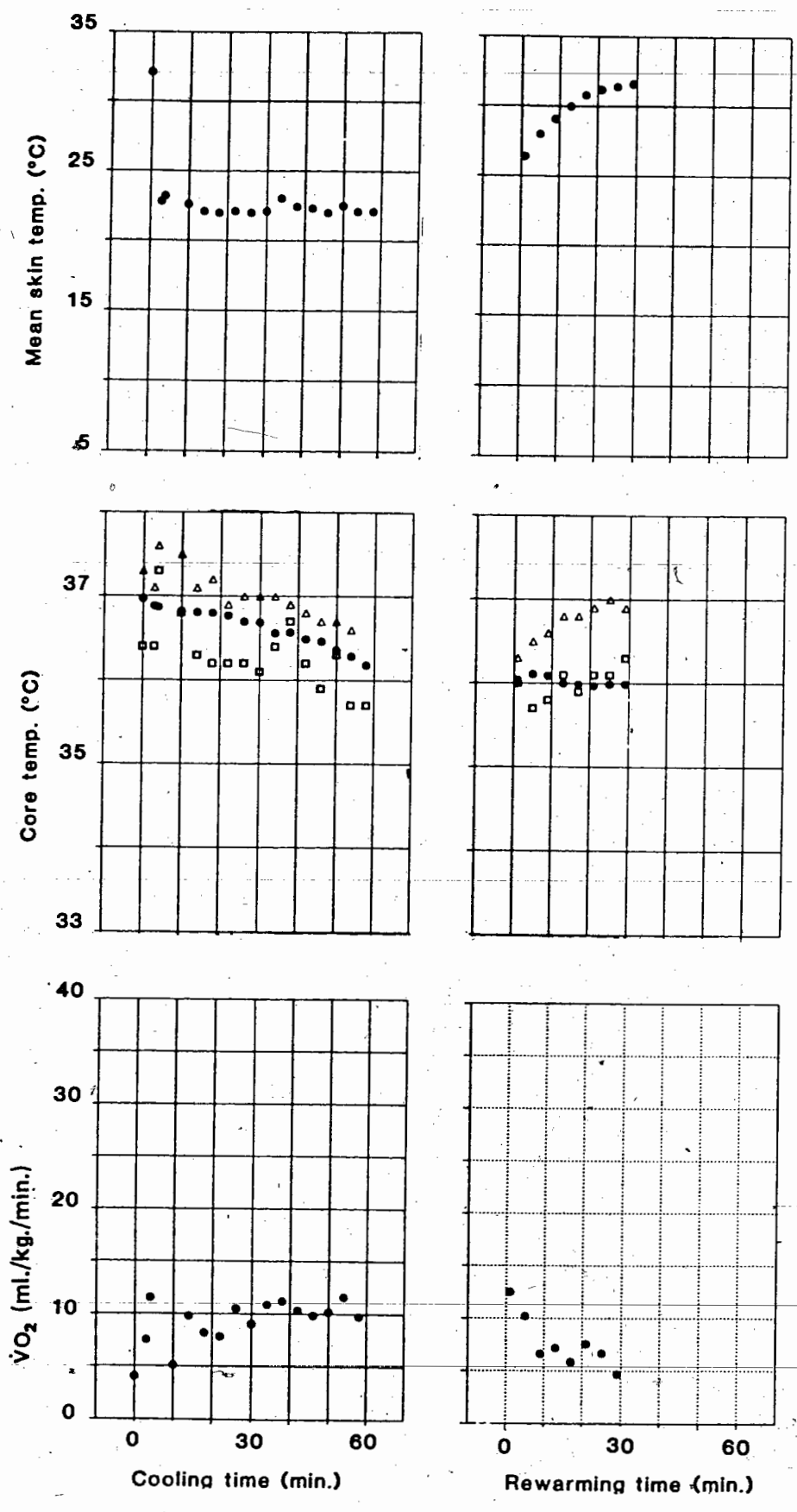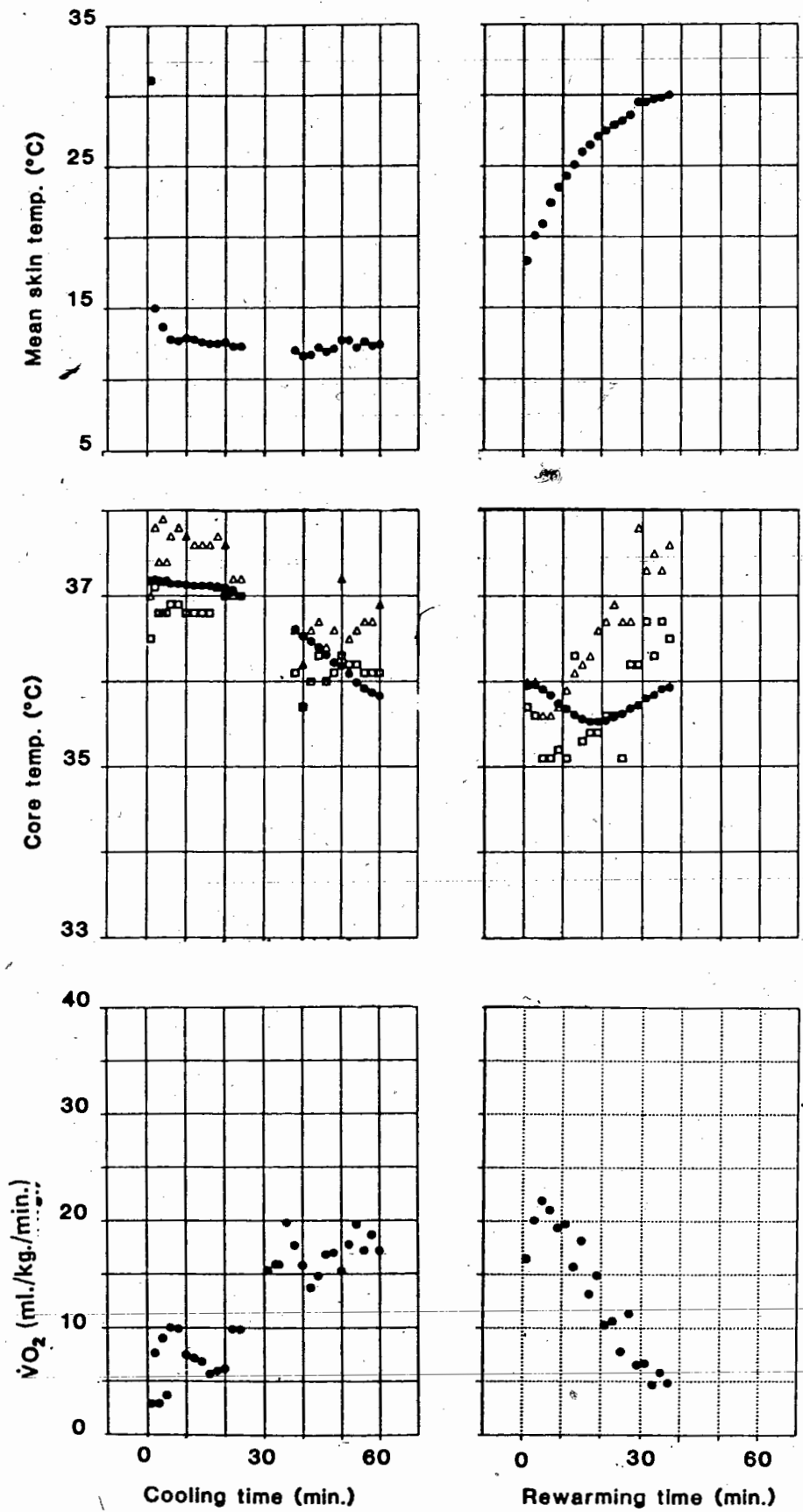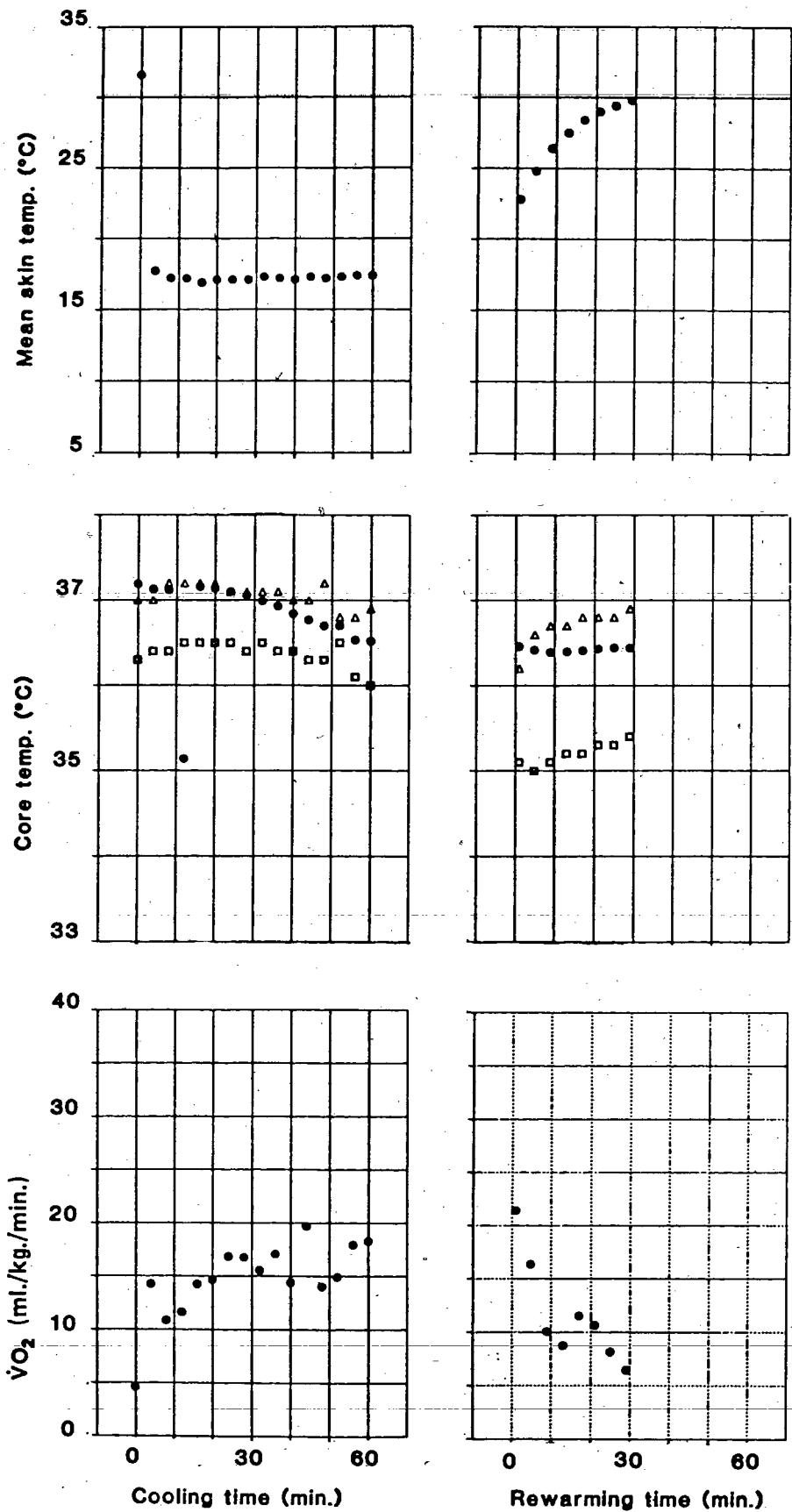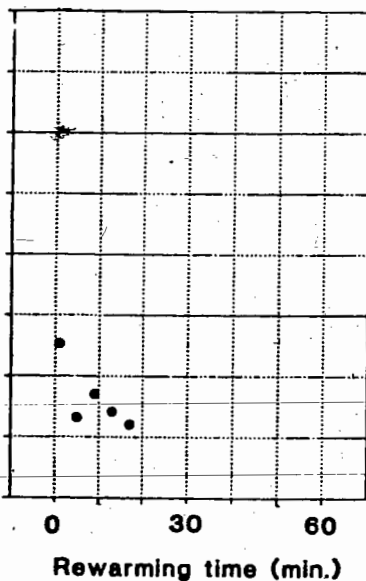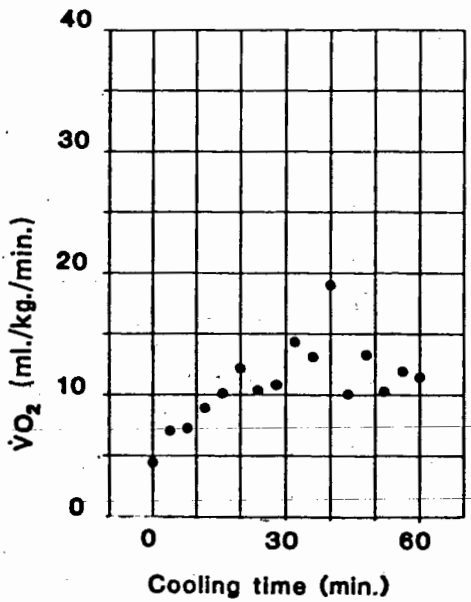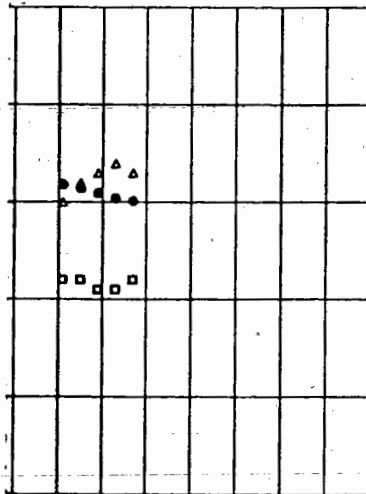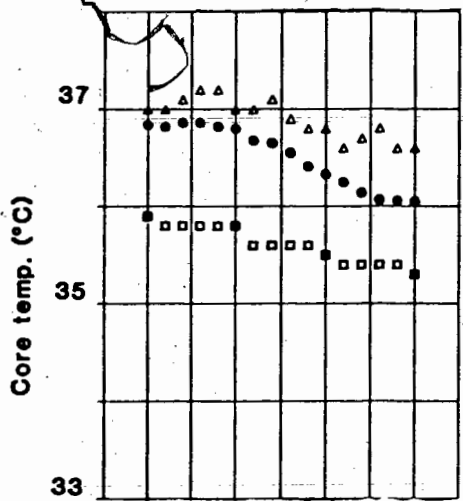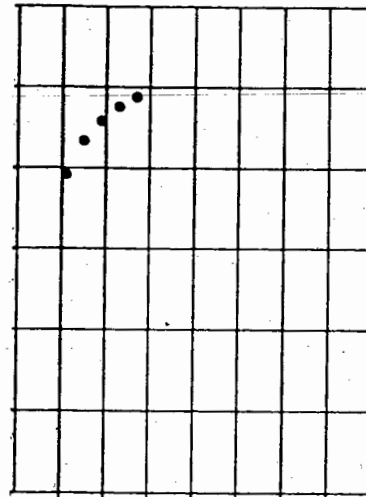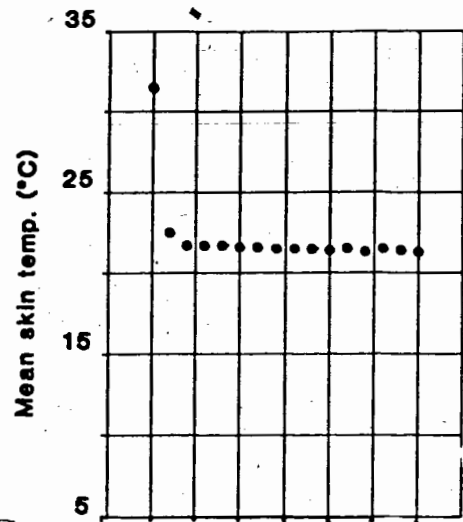
Fig. A6.5 : Subject RH

    a) RH10N

    b) RH15N

    c) RH20N

    d) RH10W

    e) RH15W

    f) RH20W

345a

345b

345c

345d

345e

345f
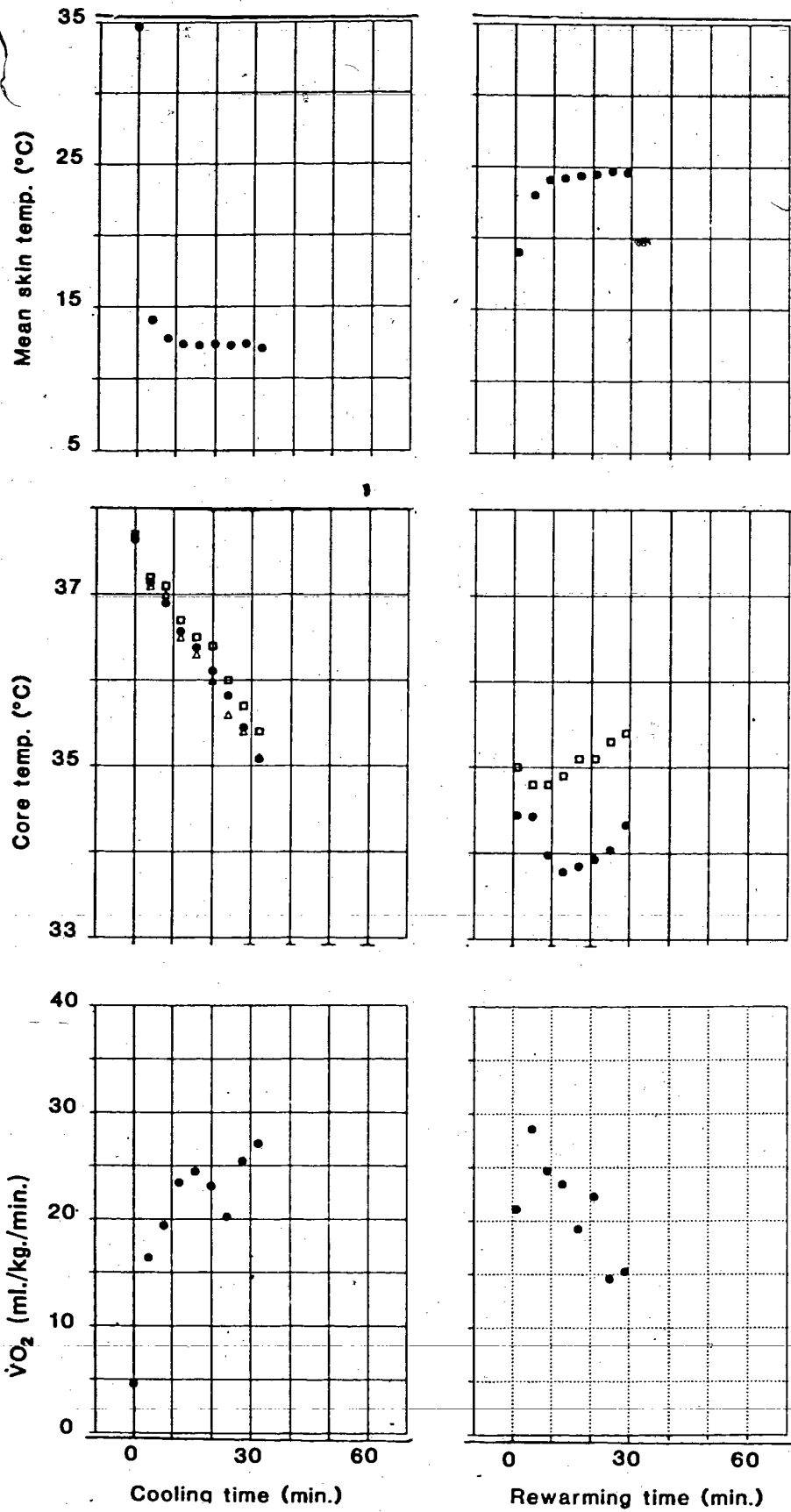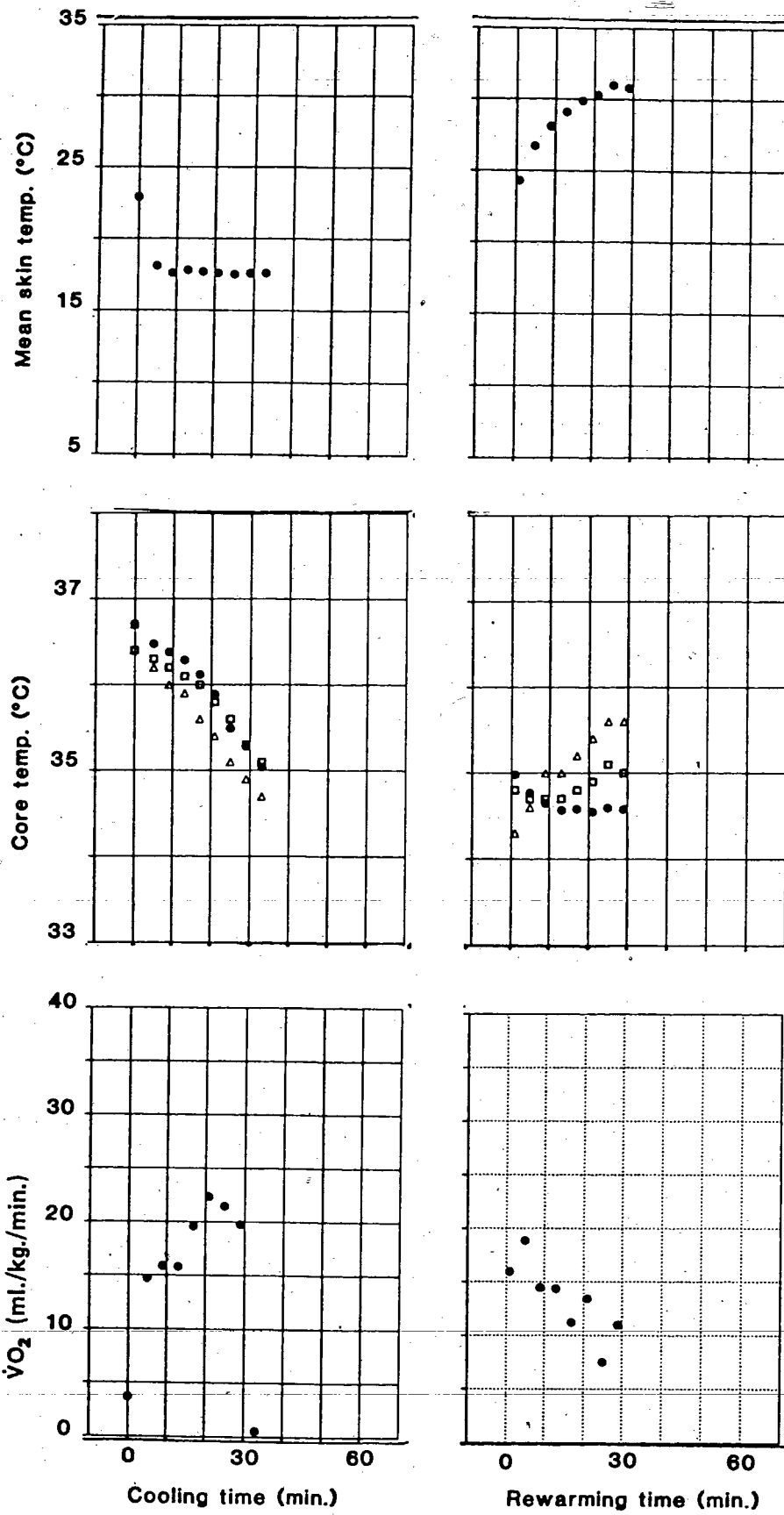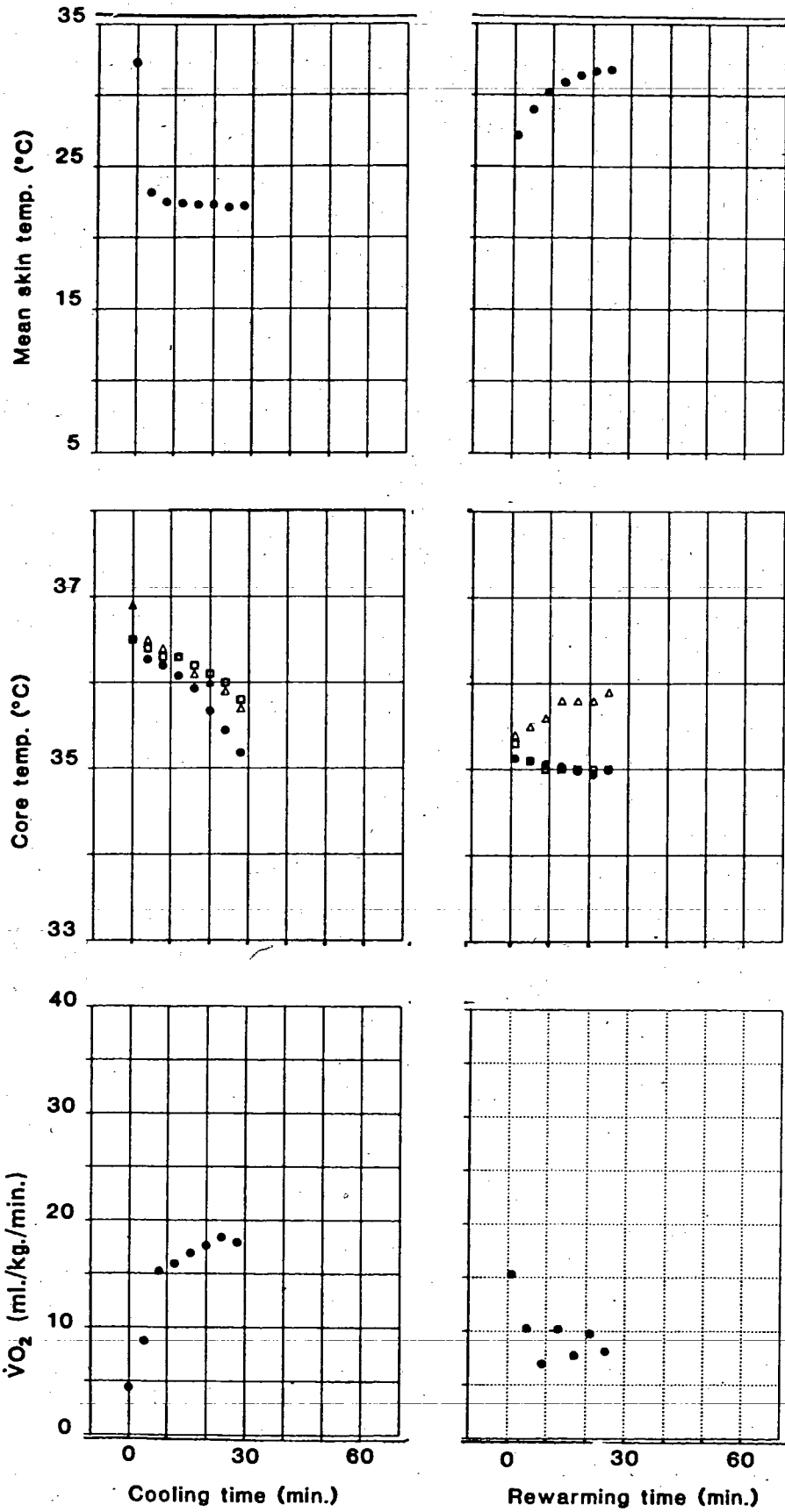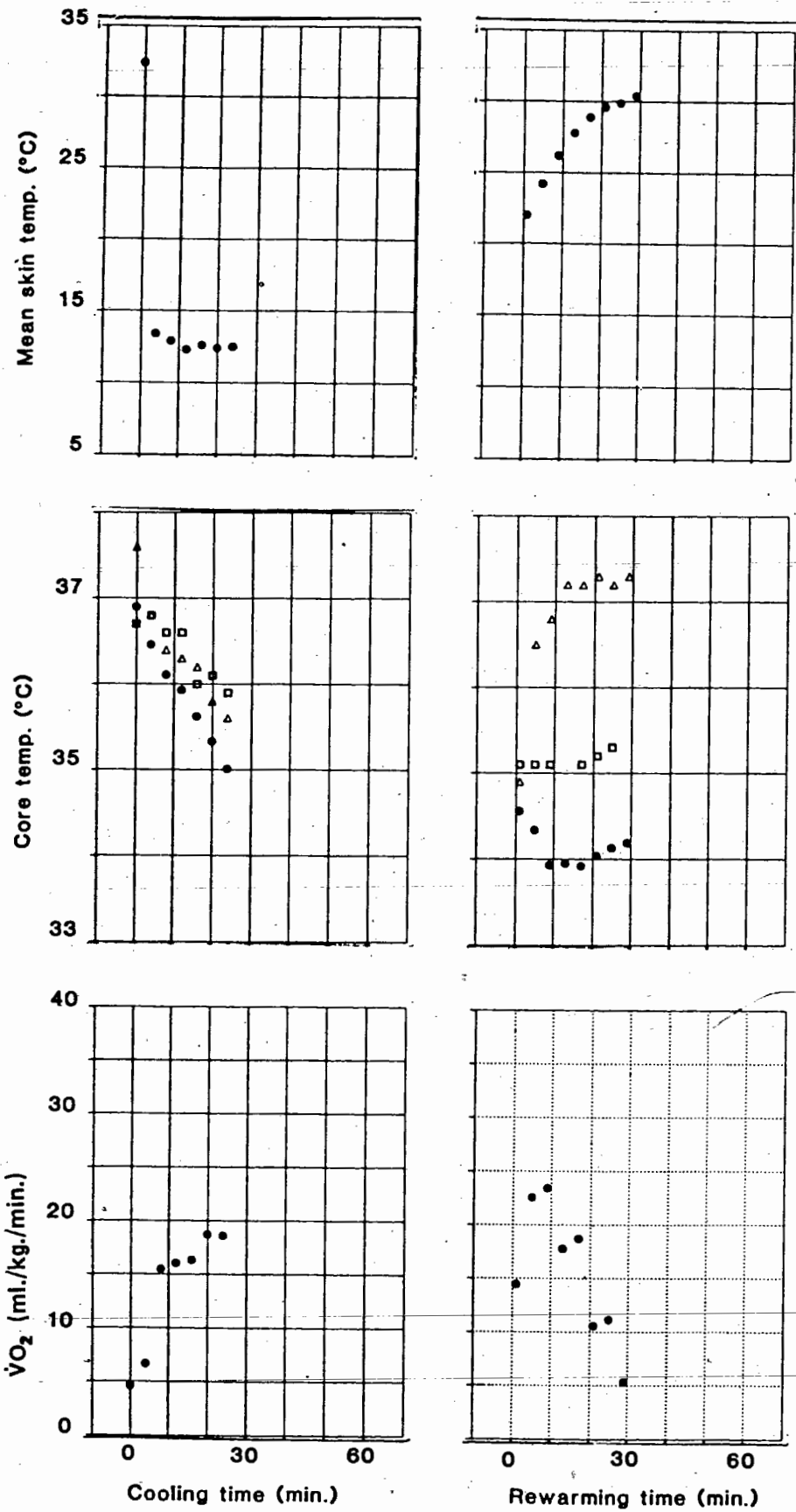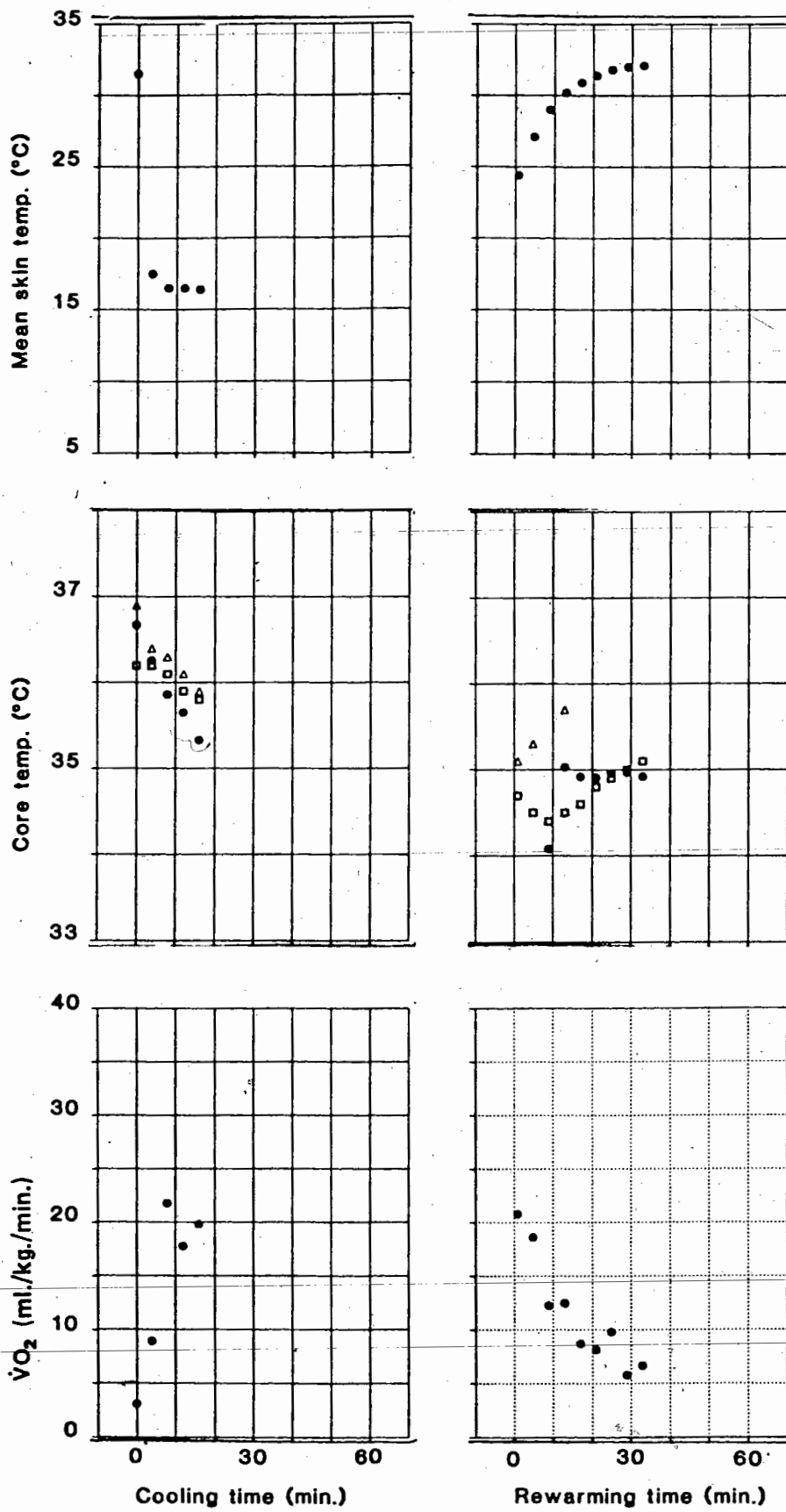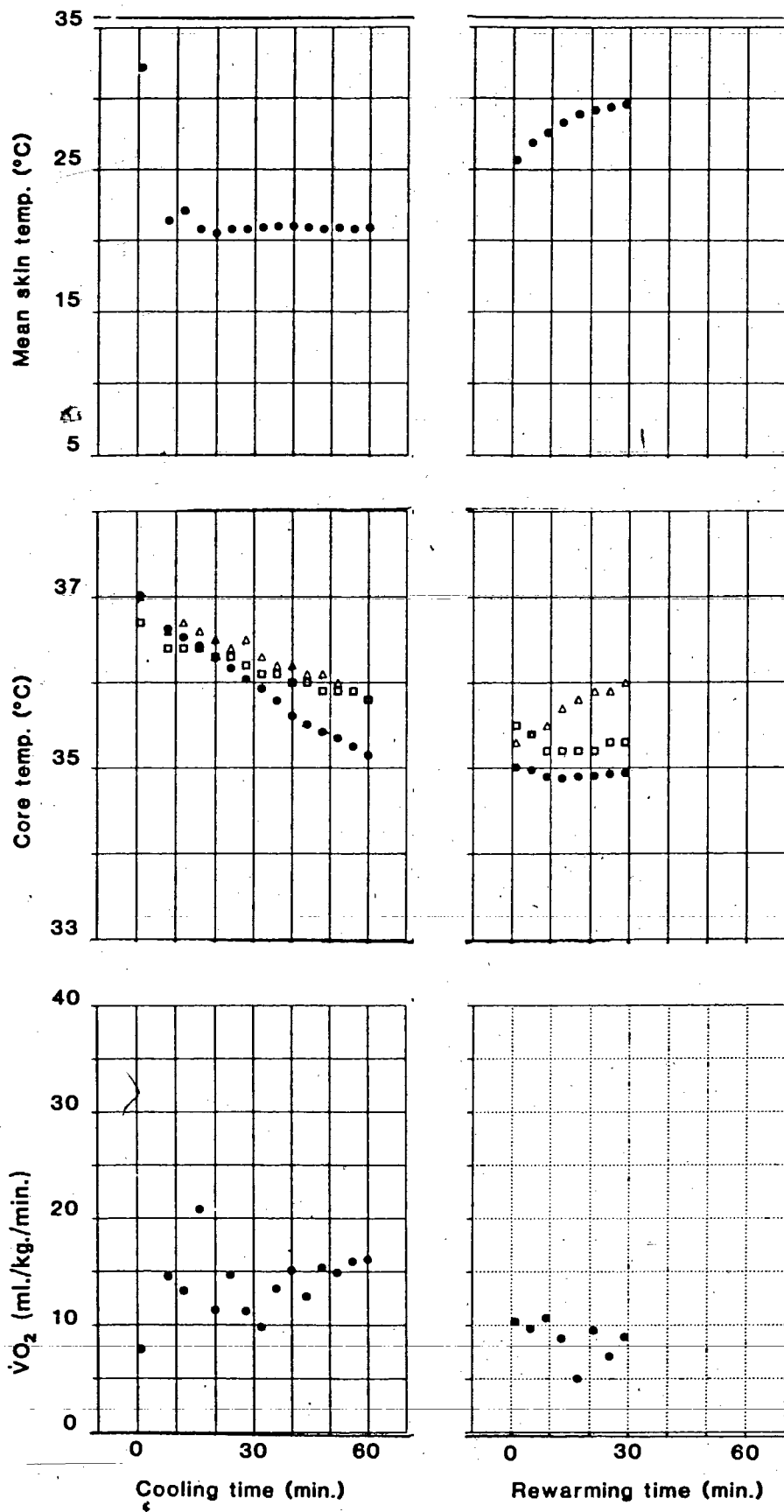
II. Heart Rate Responses during Cooling and Rewarming

Heart Rate was measured during each minute of cooling and rewarming, but only every second minute is plotted in the graphs.

Fig. A6.6 : Subject AL

    a) AL10N

    b) AL15N

    c) AL20N

Heart rate (beats/min.)

Cooling time (min.)　　Rewarming time (min.)

347b
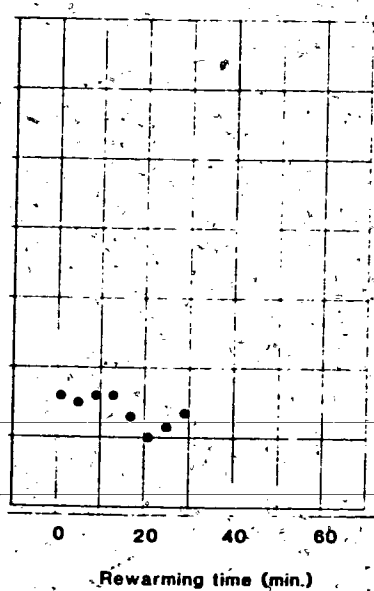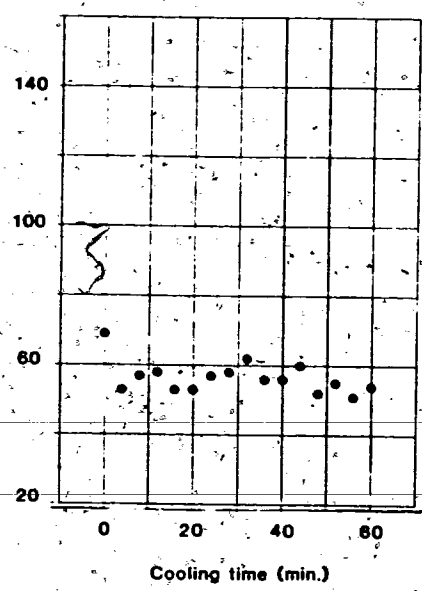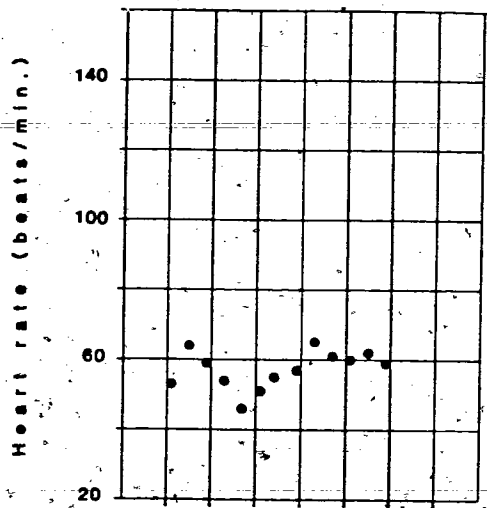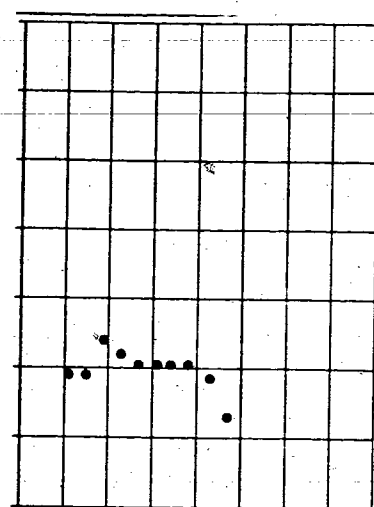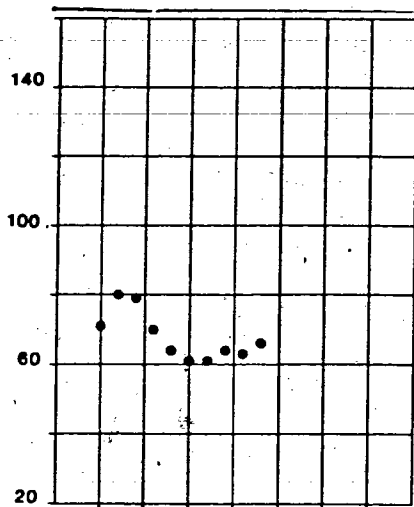
Fig. A6.7 : Subject AL

    a) AL10W

    b) AL15W

    c) AL20W

Heart rate (beats/min.)

Cooling time (min.)

Rewarming time (min.)

348b
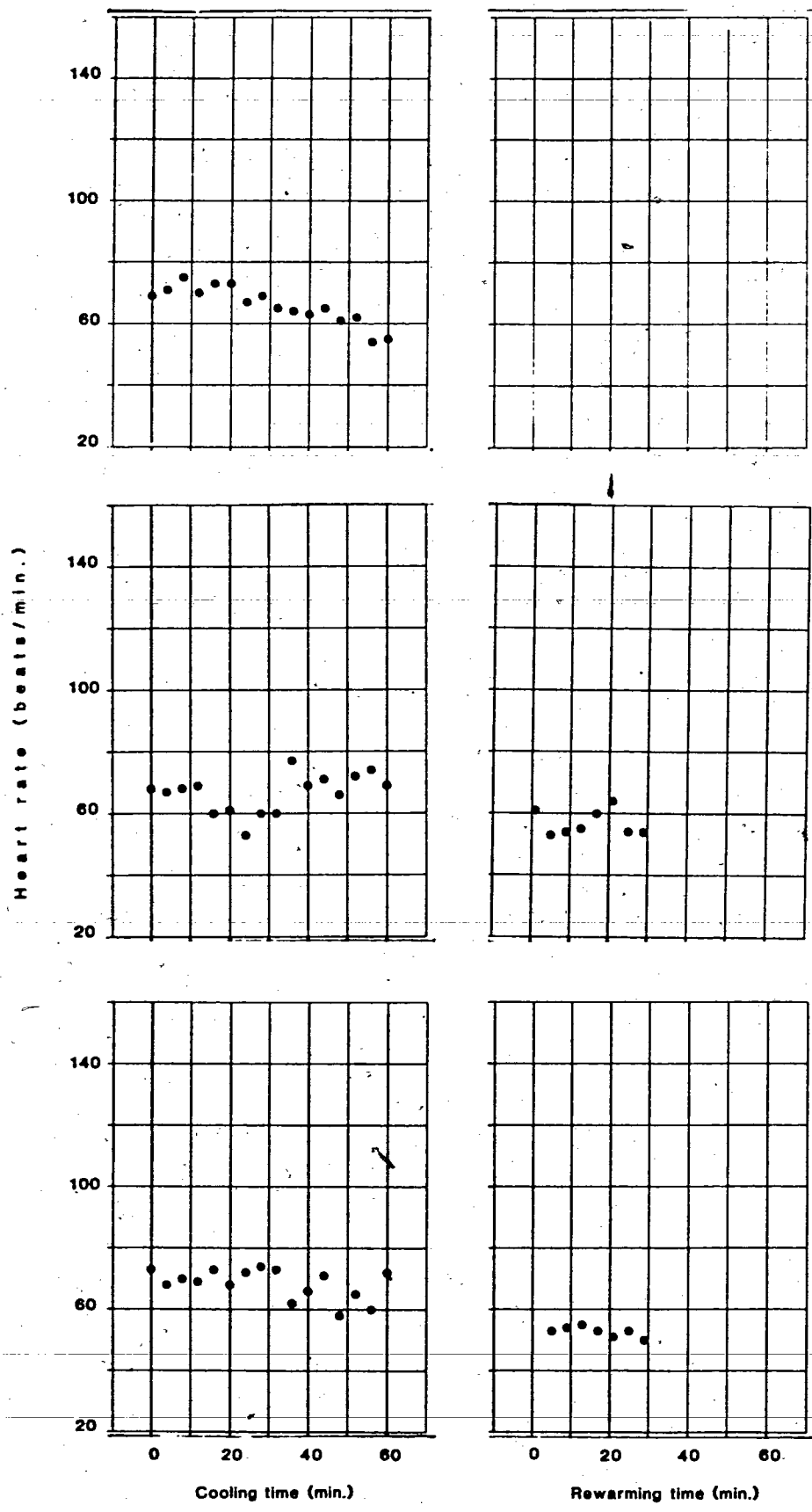
Fig. A6.8 : Subject BC

    a) BC10N

    b) BC15N

    c) BC20N

Heart rate (beats/min.)

Cooling time (min.)

Rewarming time (min.)

349b
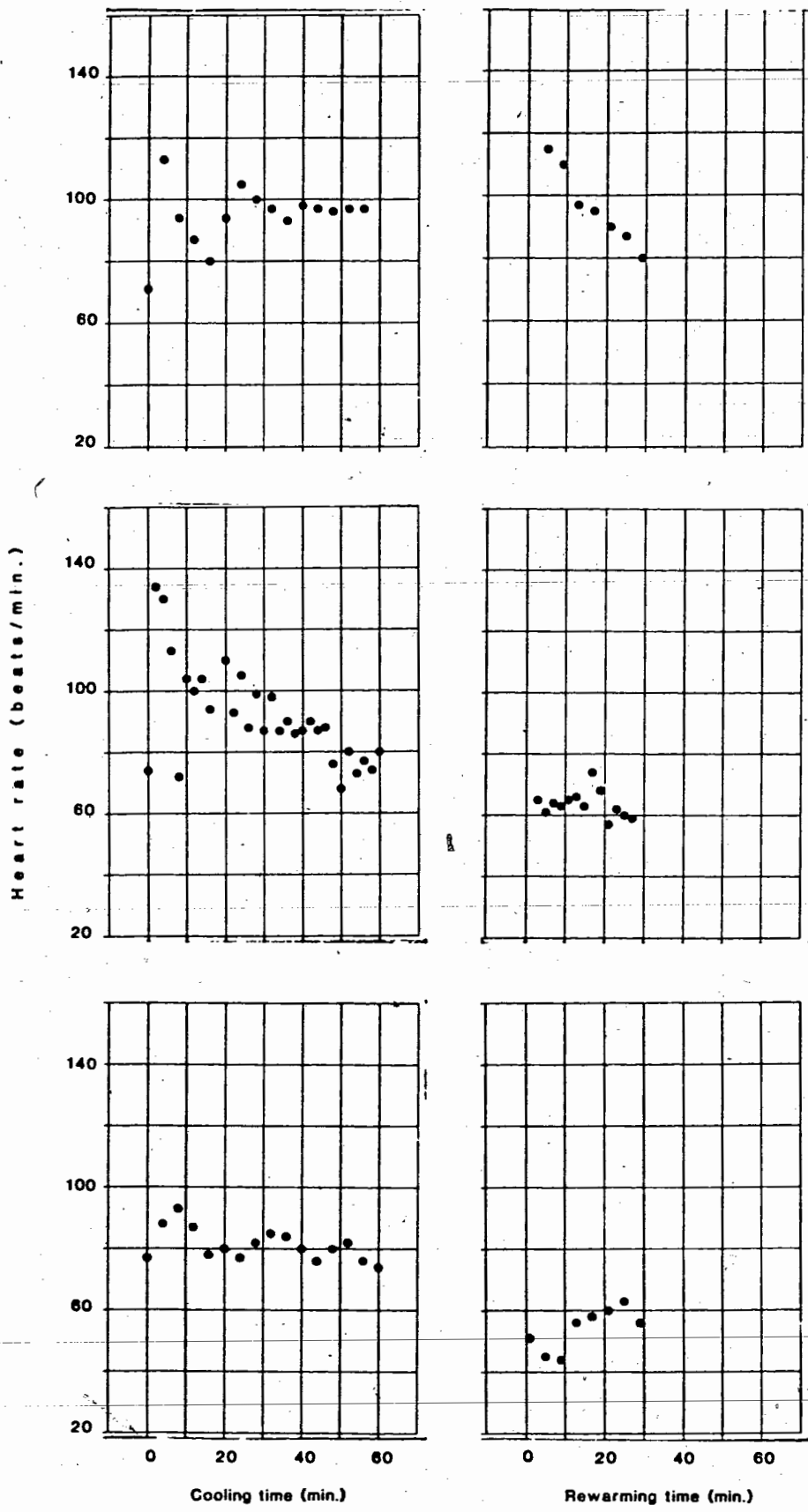
Fig. A6.9 : Subject BC

    a) BC10W

    b) BC15W

    c) BC20W

Heart rate (beats/min.)

Cooling time (min.)

Rewarming time (min.)

350b
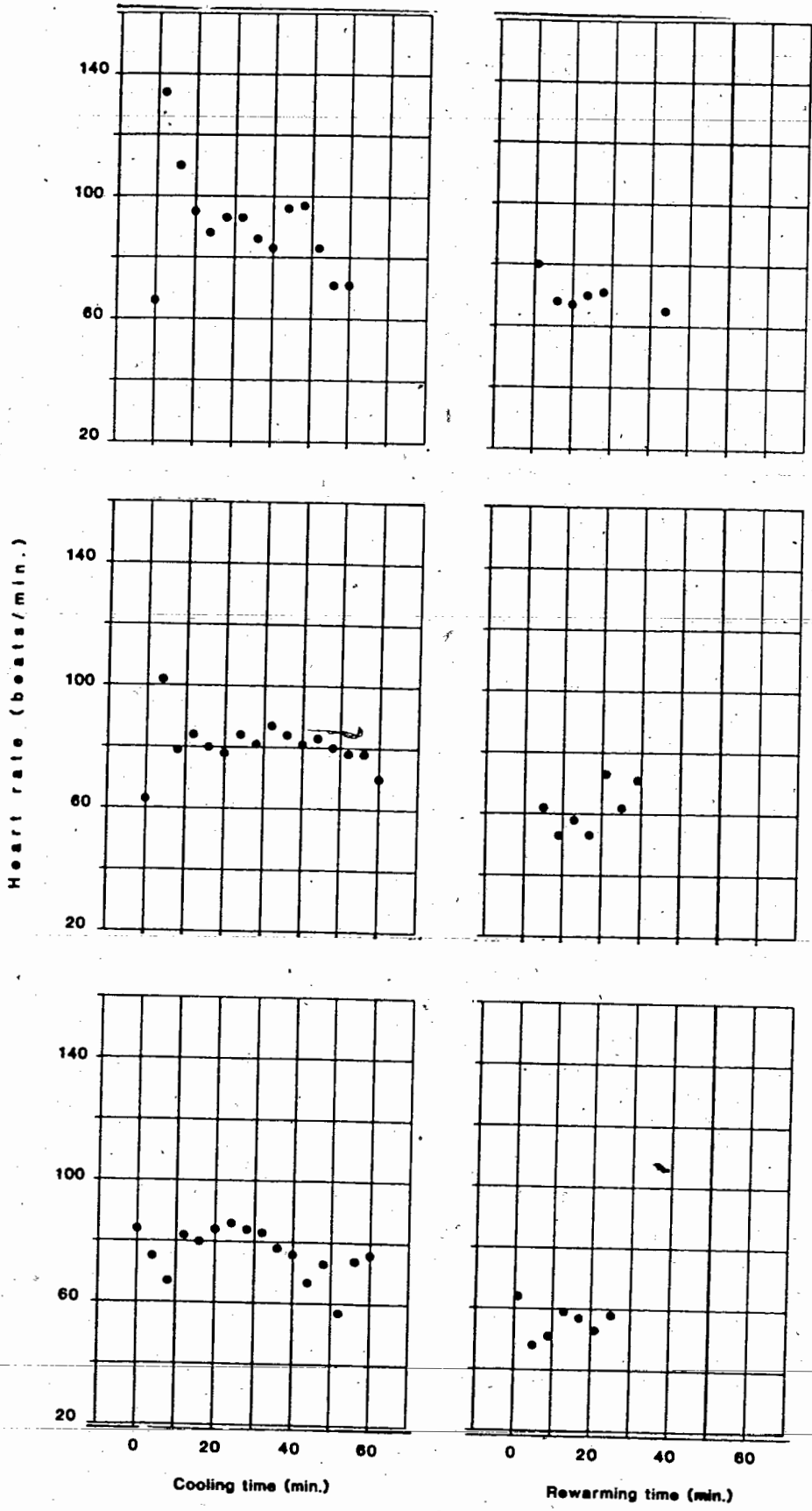
Fig. A6.10 : Subject DS

    a) DS10N

    b) DS15N

    c) DS20N

351b
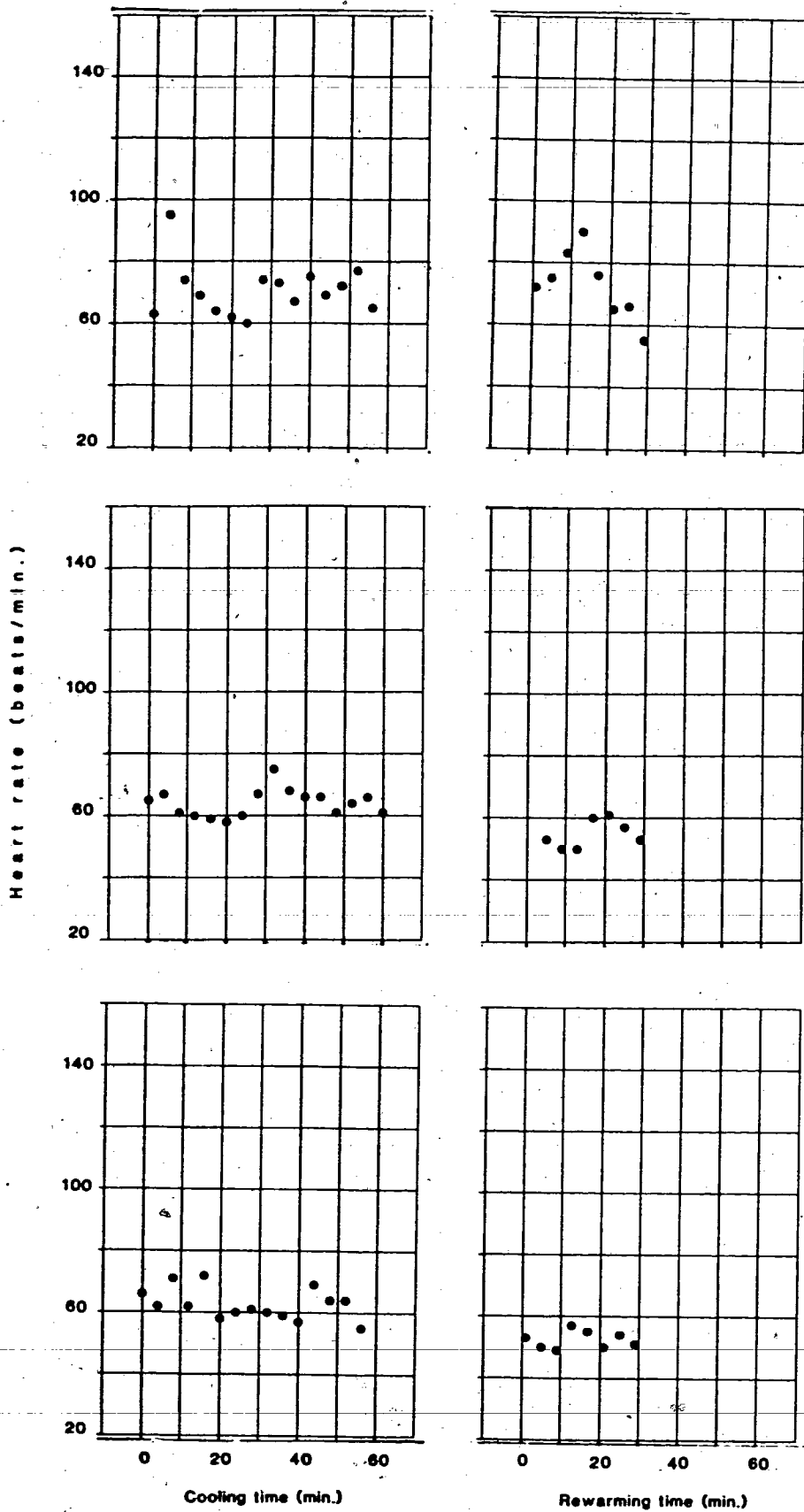
Fig. A6.11 : Subject DS

    a) DS10W

    b) DS15W

    c) DS20W

Heart rate (beats/min.)

Cooling time (min.)

Rewarming time (min.)

352b
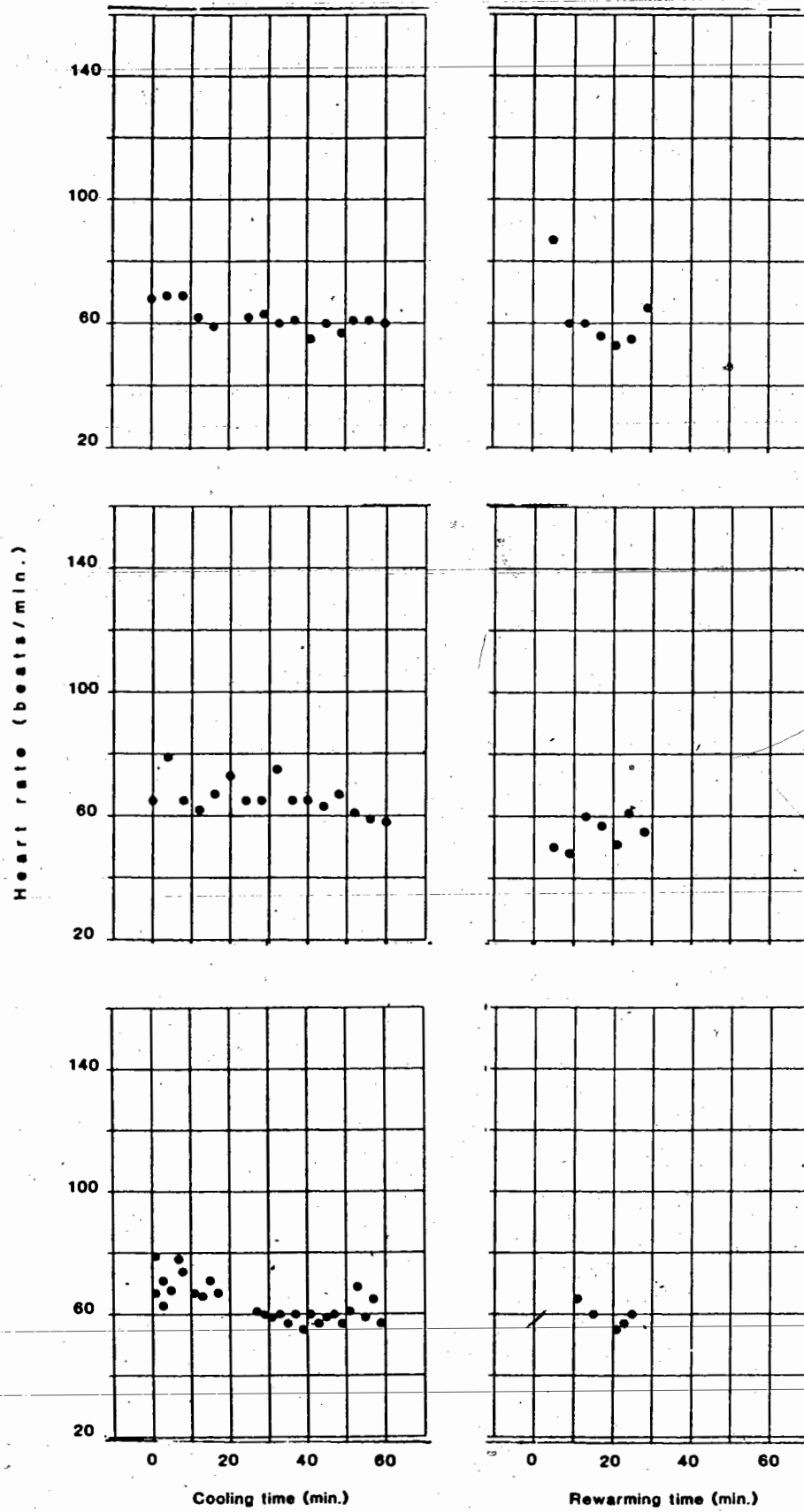
Fig. A6.12 : Subject DT

    a) DT10N

    b) DT15N

    c) DT20N

Heart rate (beats/min.)

Cooling time (min.)   Rewarming time (min.)
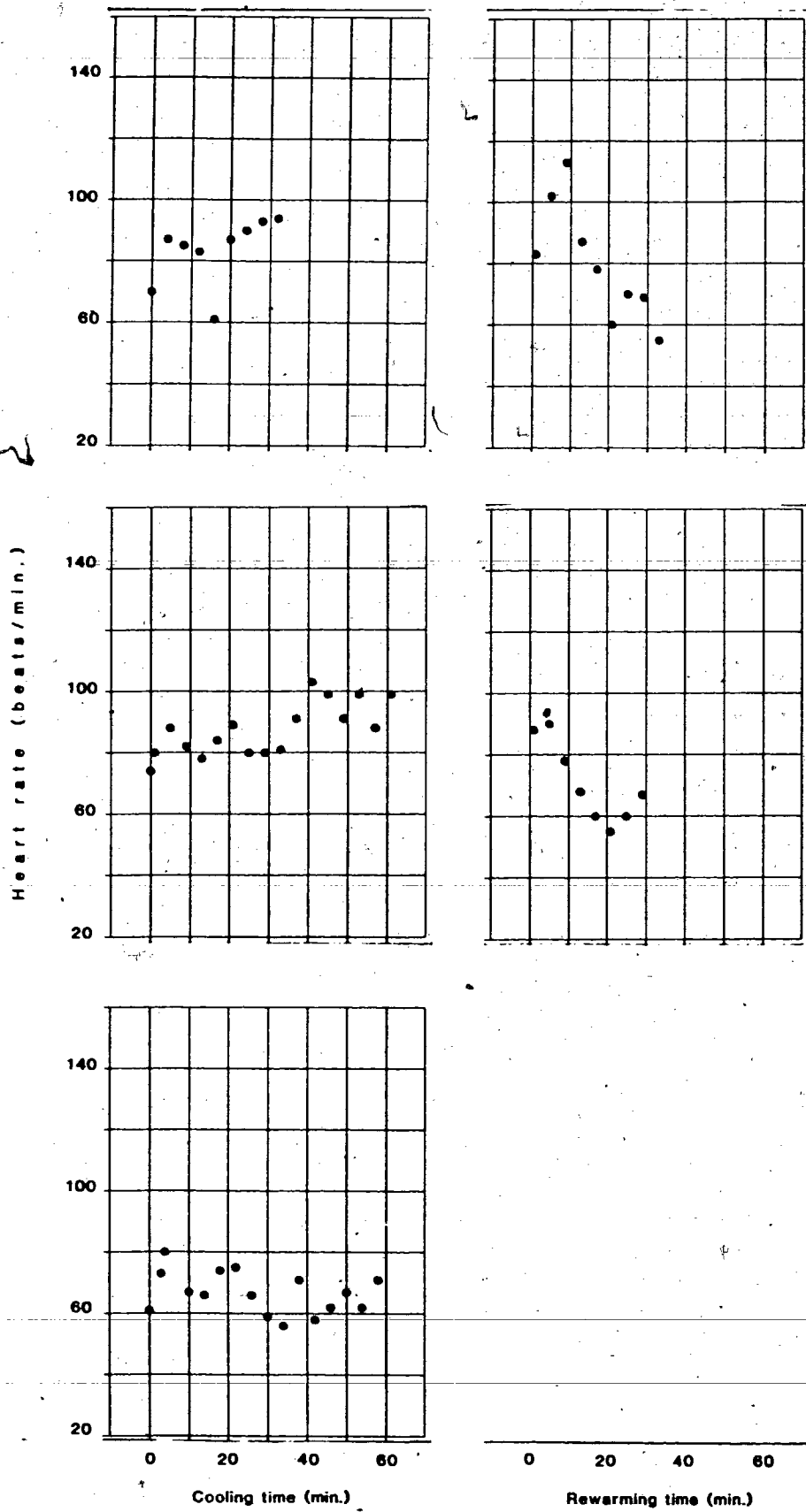
Fig. A6.13 : Subject DT

    a) DT10W

    b) DT15W

    c) DT20W

354b
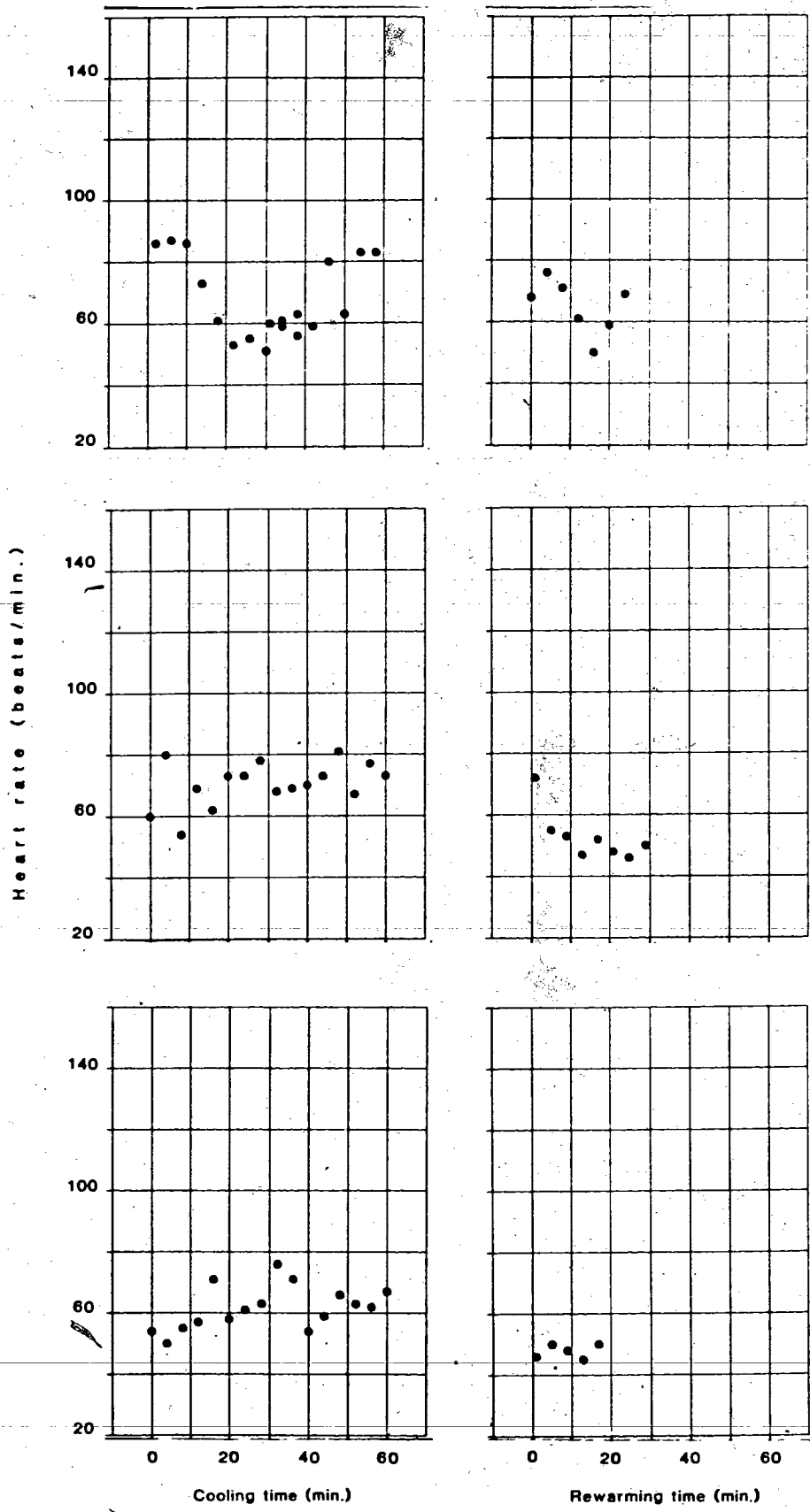
Fig. A6.14 : Subject RH

    a) RH10N

    b) RH15N

    c) RH20N

Heart rate (beats/min.)
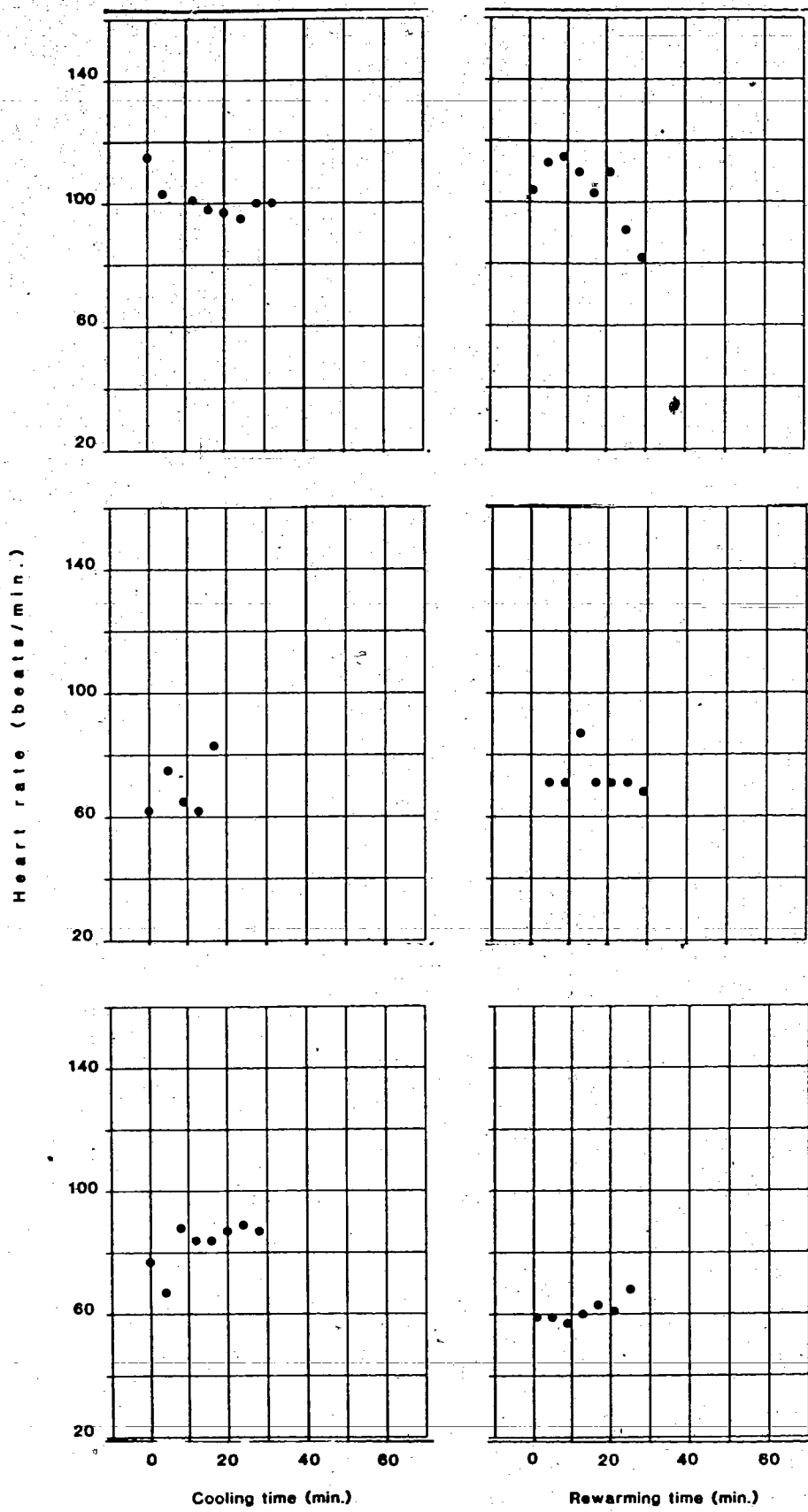
Cooling time (min.)

Rewarming time (min.)

355b

Fig. A6.15 : Subject RH

    a) RH10W

    b) RH15W

    c) RH20W

356b