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Effects of interrupting normal nasal breathing on the serum levels of thyroid stimulating hormone in the sheep

Kenneth Kurt Booth
Iowa State University

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BOOTH, KENNETH KURT

EFFECTS OF INTERRUPTING NORMAL NASAL BREATHING ON THE
SERUM LEVELS OF THYROID STIMULATING HORMONE IN THE SHEEP

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Effects of interrupting normal nasal breathing on

the serum levels of thyroid stimulating hormone

in the sheep

by

Kenneth Kurt Booth

A Dissertation Submitted to the

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DEDICATION

This dissertation is dedicated to all the very special people in my life:

to my wife, Cheryl Ann Weimer, for her many years of unselfish devotion, dedication, encouragement, and sacrifice. There just isn't a finer woman anywhere.

to my daughter, Shannon Leigh Booth, for always putting a smile on my face when times were rough and for making life worthwhile.

to my parents, Kurt H. A. Booth and Elizabeth R. Mazur, for their continued support, encouragement, and for always being there when needed.

to my grandparents, Kurt H. Booth and Lina Dzaack, and Jozsef Mazur and Maria Markovics, for unknowingly instilling a spirit to continue to better oneself in the face of hardships and unforeseen obstacles.

and finally to my co-major professor, Dr. Nani G. Ghoshal, for having the courage to take a chance.

INTRODUCTION

The blood supply to the brain, in addition to its metabolic function, acts as a cerebral coolant and as a vehicle for temperature information from the body core to the thermoregulatory center in the preoptic/ anterior hypothalamic area. The removal of heat from the brain by the blood is important since the brain has the highest rate of metabolic heat production of all body tissues (Hales, 1973) and is, at the same time, the most vulnerable to damage by hyperthermia (Burger and Fuhrman, 1964a, b).

In a neutral environment the cerebral arterial blood in all homeotherms at rest is cooler than the heat-producing nervous tissue (Baker and Hayward, 1967a,b). However, some animals (viz., the sheep, ox, pig, dog, cat, gazelle, and chicken) which possess a carotid rete, situated between the extracranial and intracranial blood supply, can maintain a brain temperature which is, on the average, 1.0° – 1.5°C below core temperature during hyperthermic conditions. In other animals with no carotid rete (viz., rat, rabbit, monkey, ape, and man), this temperature differential between cerebral blood and core blood during hyperthermia is not as great as compared to the carotid rete species.

The mechanism by which carotid rete species maintain a lower brain temperature in spite of increasing body temperature was first proposed by Magilton and Swift (1967, 1968, 1969). They observed that changes in temperatures of the angularis oculi vein and the brain paralleled temperature changes in the alar fold of dogs irrigated with warm or cold water. They hypothesized that heat is normally lost from the venous

plexuses in the nasal cavity to the ambient air ("external heat exchanger") during respiration. This cooled venous blood, in turn, drains into the cavernous sinus via the dorsal nasal, angularis oculi and ophthalmic veins, where countercurrent heat exchange results between the internal carotid rete and the cooled venous blood surrounding it ("internal heat exchanger"). This mechanism has since been demonstrated to occur in almost all carotid rete species. Cerebral cooling via heat loss from the nasal mucosa has been shown to occur in noncarotid rete species like rabbit (Kluger and D'Alecy, 1975) and is also considered possible in humans (Caputa and Cabanac, 1978; Cabanac and Caputa, 1979).

Not only the thermoregulatory center in the preoptic/anterior hypothalamic area is activated by temperature changes in the cerebral arterial blood (Forster and Ferguson, 1952; Newman and Wolstencroft, 1960; Bligh, 1963b; Baldwin and Yates, 1977), the thermal changes of this center have also been shown to affect the secretions of some pituitary hormones. Direct thermal stimulation of this area via implanted thermodes has been shown to influence the blood levels of ADH, ACTH, and TSH in a variety of animals (Itoh, 1954; Andersson et al., 1962a,b; Gale et al., 1970; Forsling et al., 1975). However, the extremes in thermode temperature (30°-42°C) needed to provoke changes in these pituitary hormone levels are well beyond the temperatures normally occurring in the body as well as beyond the levels tolerated by the body for any length of time without serious effects to vital life processes. If this thermoregulatory center does influence TSH secretion, it should provoke significant changes in TSH secretion under small variations in hypothalamic

temperatures normally occurring in the body.

The ovine hypothalamus has been reported to be the coolest portion of the brain, as it receives its entire blood supply from vessels emerging from the "internal heat exchanger" (Baker, 1972; Baker et al., 1974). Besides, Krabill (1979) was able to significantly increase temperatures around the hypothalamus in the sheep by interrupting the normal nasal breathing which reflected in a decreased efficiency of the countercurrent heat exchange mechanism within the cavernous sinus. In view of the above, this study was undertaken to test the hypothesis that interruption in normal nasal breathing, which would derange the efficiency of heat exchange within the cavernous sinus and thus increase the local temperature around the hypothalamus, will affect the serum levels of TSH in the nonstressed sheep.

This same mechanism of brain temperature regulation is also believed to occur in humans; thus, this work may have application particularly in mongoloids (Down's syndrome) whose nasal air flow, to some extent, is impaired by the underdevelopment of the facial bones and who have been shown to have a variety of endocrine dysfunctions of the hypothalamus and/or pituitary gland (Murdoch et al., 1977). Also endocrine changes may be present to a varying degree in people with permanent tracheostomies, however, possible endocrine changes in these people as compared to normal nasal breathers have not yet been investigated.

LITERATURE REVIEW

Brain Temperature and Its Regulation

Since the brain produces the greatest amount of heat among all body tissues (Hales, 1973) and it is also the most vulnerable to damage by hyperthermia (Minard and Copman, 1963; Burger and Fuhrman, 1964a,b; Frascella and Frankel, 1969; Kuchereko, 1970; Nemoto and Frankel, 1970; Wells, 1973; Bowler and Tirri, 1974; Caputa et al., 1976a,b; Carithers and Seagrave, 1976), the regulation of brain temperature is of primary concern to any homeotherm. Serota and Gerard (1938) and Rawson and Hammel (1963) stated that brain temperature in mammals is a function of four variables, viz., the rate of metabolic heat production, the arterial blood temperature, the rate of blood flow, and the rate of heat conduction. The rate of heat production is an important determinant of brain temperature; however, studies have shown that the temperature of the brain is primarily controlled by the rate of heat removed from the brain by the cerebral arterial blood in the rat (Abrams and Hammel, 1964; Abrams et al., 1965), rabbit (Kahn, 1904; Heymans, 1921; Baker and Hayward, 1967a; Findlay and Hayward, 1969; Caputa et al., 1976a,b), cat (Newman and Wolstencroft, 1956, 1960; Holmes et al., 1960; Baker and Hayward 1967b; Baker, 1972), dog (Moorhouse, 1911; Jelsma, 1930; Hammel et al., 1958; Hayward, 1968; Baker et al., 1974; Baker and Chapman, 1977), sheep (Baker and Hayward, 1968a,b,c,d; Baldwin and Yates, 1977), ox (Ingram and Whittow, 1962a,b, 1963), and monkey (Rawson and Hammel, 1963; Hayward et al., 1965, 1966; Hayward, 1967; Hayward and Baker, 1968a,b, 1969). These investigators discovered that thermal shifts in brain temperature paralleled

thermal shifts in cerebral arterial temperature.

The heat removal capability of the cerebral blood is a function of its temperature and rate of flow. Serota and Gerard (1938) suggested that, for heat to be removed from the brain, the arterial blood supply must be cooler than the brain tissue which has been shown to be true in different mammals (Hayward et al., 1966; Baker and Hayward, 1967a,b, 1968d; Hayward, 1968; Hayward and Baker, 1968b, 1969; Baker, 1972; Baker et al., 1974). These investigators reported that a gradient of increasing temperature exists from the cerebral arteries to the center of the brain in all mammals. In addition, Hammel et al. (1963) and Hayward and Baker (1968a,b, 1969) demonstrated in the monkey that hypercapnia, which caused a dilatation of cerebral blood vessels due to an increase of arterial CO_2 tension, enhanced the flow of cooler arterial blood through the brain and accelerated the process of brain cooling, while during hypocapnia, which produced vasoconstriction, there was a decrease in cerebral blood flow and an increase in brain temperature. Thus the cerebral blood, in addition to its nutritive function, acts as a cerebral coolant.

Carotid Rete vs. Noncarotid Rete Species

Although the cerebral arterial blood in all homeotherms at rest in a neutral environment is cooler than the heat-producing nervous tissue (Baker and Hayward, 1967a), the cooling of the brain by the cerebral blood in a hyperthermic environment or during excessive exercise varies among species. For example, the cerebral arterial blood in species with a carotid rete like the sheep, ox, dog, cat, gazelle, chicken, and rhea

have been shown to be, on the average, 1.0-1.5°C cooler than the blood at
the aortic arch during heat-stressful conditions, while in noncarotid
rete species like the rat, rabbit, monkey, and humans, the ·temperature
differential between the cerebral arterial blood and the core was not as
great during hyperthermia (Hayward et al., 1966; Hemingway et al., 1966;
Hunter and Adams, 1966; Baker and Hayward, 1967a, 1968a,b; Hayward and
Baker, 1969; Hayward, 1967; Richards, 1970; Baker, 1972; Taylor and Lyman,
1972; Baker and Chapman, 1977; Cabanac and Caputa, 1979).

Daniel et al. (1953) described the carotid rete as a compact network
of intertwined, freely anastomosing arteries interposed along the course
of the internal carotid artery, which lay within a venous sinus. In the
ox, sheep, goat, and pig, the rete is situated intracranially within the
cavernous sinus, which receives cooled venous blood from the cranial and
nasal areas; in the cat, however, the rete is situated extracranially
within the pterygoid plexus (Baker and Hayward, 1968a; Hayward and Baker,
1969). Daniel et al. (1953) also found that in those species with a well
developed carotid rete (viz., the ox, sheep, goat, pig and cat), the
extracranial segment of the internal carotid artery is either regressed
or entirely absent. The intracranial segment of the internal carotid
artery persists, representing the efferent vessel of the carotid rete,
which pierces the dura and contributes to the formation of the cerebral
arterial circle (Baldwin and Bell, 1963; Baldwin, 1964). In the dog,
which has a rudimentary carotid rete, the internal carotid artery passes
through the intracranial cavernous sinus, receiving only a few rete
branches, while in the noncarotid rete species (rat, rabbit, monkey,

human), the int..rnal carotid artery passes through the sinus as a single vessel (Daniel et al., 1953). In the cat, sheep, goat, and ox, the carotid rete is formed by the rostral and caudal rete branches of the maxillary artery, while in the pig, the major contribution is via the ascending pharyngeal artery (Daniel et al., 1953). In addition, the carotid rete, in the ox and sheep, can receive blood from the occipital and vertebral arteries via contributions from the basi-occipital plexus (Baldwin and Bell, 1963; Baldwin, 1964).

Mechanism of Brain Temperature Regulation

Since most mammals pant upon exposure to heat (Baker and Hayward, 1968c, Bligh, 1966; Robertshaw, 1976), many researchers have investigated the possible role of the nasal cavity in brain temperature regulation. Cole (1954) noted that the temperature of inspired air is normally raised close to body temperature in the upper respiratory tract. Mather et al. (1953) and Bligh (1957b,c) found no change in the temperature of the blood which traversed the lungs during panting, while Ingram and Whittow (1962a,b) demonstrated in the ox that the cranial blood cooling occurred in the upper respiratory tract with panting. Investigations in the dog (Hammel et al., 1958; Jackson and Hammel, 1963; Hellstrom and Hammel, 1967; Baker et al., 1974; Baker and Chapman, 1977), cat (Forster and Ferguson, 1952; Baker, 1972), sheep (Bligh, 1959, 1963b; Hemingway et al., 1966; Hayward and Baker, 1969; Rawson and Quick, 1972; Young et al., 1976), ox (Brody, 1948; Findlay and Ingram, 1961; Ingram and Whittow, 1962a,b), gazelle (Taylor, 1969), antelope (Taylor and Lyman,

1972), rabbit (Caputa et al., 1976a,b), and domestic fowl (Randall, 1943; Richards, 1970) demonstrated that increases in respiratory rate during heat exposure resulted in significant cooling of the brain. Baker and Chapman (1977) stated that the degree of brain cooling in exercising dogs, due to increased nasal ventilation, is almost three times as great as dogs at rest. In addition, shifts in brain temperature have been found to be associated with changes in heat loss from the nasal mucosa in the cat (Baker, 1972), sheep (Baker and Hayward, 1968a,b), and monkey (Hayward and Baker, 1968b). Hunter and Adams (1966) believed that in the cat, convective and evaporative heat losses from the upper respiratory tract had a direct cooling effect on the brain.

Magilton and Swift (1967, 1968, 1969), while irrigating the alar fold of the dog with warm and cold water, observed parallel increases and decreases, respectively, in the temperature of the angularis oculi vein and in the brain. From this they hypothesized that the fluctuations in brain temperature resulted from the transfer of heat from the venous plexuses in the nasal mucosa ("external heat exchanger") to the ambient air. This cooled venous blood, in turn, drains into the cavernous sinus of the dog via the dorsal nasal, angularis oculi, and ophthalmic veins, where countercurrent heat exchange results between the internal carotid rete and the cooled venous blood surrounding the former ("internal heat exchanger"). This concept of countercurrent heat exchange between blood in the carotid rete and cavernous sinus is supported by similar observations in the dog (Baker and Chapman, 1977), cat (Baker and Hayward, 1967b), sheep (Baker and Hayward, 1968a,b,c,d) and gazelle (Scott, 1954).

Blatt et al. (1972) described that the secretions of the lateral nasal gland, in the dog, increased in hot environments and accounted for almost half of the evaporative heat loss during panting. In addition, similar to the vasomotor responses controlling the rate of blood flow through the skin and thereby regulating heat loss, vasoconstriction and vasodilatation of the nasal vessels have been shown to decrease and increase, respectively, evaporated heat loss from the nasal mucosa, which increased and decreased, respectively, brain temperature in the rabbit (Caputa et al., 1976b), cat (Baker, 1972), sheep (Baker and Hayward, 1968a,b), and monkey (Hayward and Baker, 1968b). These investigators reasoned that vasoconstriction of the nasal mucosa resulted in a reduced flow of cooled venous blood toward the cavernous sinus, affecting an optimum countercurrent heat exchange between arterial and venous blood in the area and, thus, increasing the brain temperature. Vasodilatation, on the other hand, increases the flow of cool venous blood from the nasal area to the cavernous sinus, resulting in an efficient countercurrent heat exchange and thereby decreasing the brain temperature. Further evidence of evaporative cooling in the nasal cavity has been obtained from studies in the ox, sheep, goat, rabbit, pig, cat, and dog, which demonstrated a linear relationship between available humidity level of the inspired air and the respiratory frequency (Sihler, 1880; Lee et al., 1941; Lee and Robinson, 1941; Robinson and Lee, 1941a,b,c; Riek et al., 1950; Beakley and Findlay, 1955; Bligh, 1957a, 1959, 1963a,b; Baker and Hayward, 1968a). These investigators observed that raising the humidity of hot, dry inspired air caused a marked increase in respiratory rate. They reasoned that

increased humid-ty lowered the evaporative heat loss at the nasal mucosa
which, in turn, caused a rise in the brain temperature, provoking an
increase in respiratory ventilation in an attempt to cool the brain.

Heat loss at the nasal mucosa depends not only upon the rate of
blood flow through its surface but also upon the rate and pattern of air
flow over its surface (Baker, 1972). During panting, air is drawn
rapidly across the nasal mucosa and heat is lost from the mucosa by con-
vection and vaporization (Scott, 1954). According to Negus (1949), the
majority of animals pant with their mouths closed because the epiglottis
normally lies along the nasal surface of the soft palate and thus pre-
vents mouth breathing. True mouth breathing is only possible in apes
and man, where the larynx opens into the oropharynx instead of the naso-
pharynx. The unidirectional airflow in panting dogs, which tend to
breath in through the nose and out through the mouth, allows maximum
evaporation to occur from the nasal mucosa (Schmidt-Nielsen et al., 1970)
and eliminates almost twice as much heat (Scott, 1954). The essential
feature of rapid shallow breathing during panting (Anrep and Hammouda,
1933) is that it provides the most efficient means of increasing ventila-
tion in the nasal cavity without increasing alveolar ventilation
(Robertshaw, 1976), tidal volumn (Whittow et al., 1964; Schmidt-Nielsen
et al., 1970) or changing the blood-gas balance (Whittow et al., 1964).
Although Albers (1961) and Siemon et al. (1966) reported substantial
increases in oxygen consumption in panting dogs and Gonzalez et al. (1971)
believed that panting causes increased metabolic heat production, Hammel
et al. (1958) and Crawford (1962) found that heat production during panting

in the dog is minimal since dogs pant at the resonant frequency of the respiratory system, thereby maintaining air flow with the least effort. In addition, Whittow and Findlay (1968) estimated that the oxygen cost of panting in the ox represented only 11% of the total oxygen consumption.

Studies in the rabbit (Kluger and D'Alecy, 1975; Caputa et al., 1976a), dog (Baker et al., 1974), cat (Hunter and Adams, 1966), and sheep (Young et al., 1976; Krabill, 1979) provided additional support for the concept that nasal air flow is necessary for the brain temperature regulation. When these investigators interrupted normal nasal breathing either by mechanical or chemical means, there was an immediate increase in the brain temperature. Conversely, resumption of normal nasal breathing caused an immediate drop in brain temperature. In addition, Dixon et al. (1949) and Toppozada and Gaafar (1976) found that the temperature of the nasal mucosa in tracheostomized humans was 1.2°C higher than that of the normal and they attributed this to the absence of normal air flow through the nasal cavity. Krabill (1979) observed a similar effect in the sheep when normal nasal breathing was interrupted by a chronic implant of an upper respiratory bypass cannula into the trachea.

Investigations have shown that heat loss in the nasal cavity is also important in brain temperature in noncarotid rete species. Panting in the rabbit has been shown to lower brain temperature by as much as 0.5°C during hyperthermic conditions (Kluger et al., 1973; Kluger and D'Alecy, 1975; Caputa et al., 1976a,b). Nasal mucosal vasodilatation and vasoconstriction have been observed to decrease and increase, respectively, the brain temperature in rabbits, similar to that observed in carotid

rete species (Kluger and D'Alecy, 1975; Caputa et al., 1976a,b). Since
the ophthalmic and pterygoid venous plexuses receive cool blood from the
nasal cavity and the temperature changes in these plexuses, caused by
nasal vasomotor changes, paralleled the temperature changes in the brain,
the above investigators suggested that selective cooling of the rabbit's
brain primarily occurs via conductive heat exchange from the brain through
the cranial vault to the venous blood in these plexuses. Besides, a
limited amount of countercurrent heat exchange may also occur within the
cavernous sinus of the rabbit (Kluger and D'Alecy, 1975). In humans,
the same veins that drain the nasal cavity in carotid rete species, the
ethmoidal and sphenopalatine veins, communicate with the cavernous sinus
via the ophthalmic veins and the pterygoid venous plexus, respectively
(Baker and Hayward, 1968a). Also, Ralston and Kerr (1945) and Scott
(1954) observed that in a warm environment the nasal mucosal vessels of
humans dilate, while in cold environments they constrict. Dixon et al.
(1949) found that the mucosal vessels of the nose in laryngectomized
humans were congested and the surface temperature of the nasal cavity was
1.2°C higher than in the normal person. They stated that these effects
were due to the lack of ventilation in the nose. When compressed air was
blown into the nose of these patients, the surface temperature immediately
dropped 5°-8°C. A similar change in mucosal temperature was observed by
Krabill (1979) when normal nasal breathing was resumed in the sheep after
a prolonged interruption. In addition, Caputa and Cabanac (1978) and
Cabanac and Caputa (1979) believed that selective cooling of the human
brain, as a protection against overheating, can occur in a similar manner,

as that proposed by Magilton and Swift (1967, 1968, 1969), for carotid rete species.

Effects of Hypothalamic Temperature

Temperature changes around the hypothalamus, particularly the pre-optic/anterior hypothalamic region, have been demonstrated to elicit thermoregulatory responses of the body. Studies in the rat, rabbit, dog, cat, ox, sheep, goat, pig, monkey, and baboon showed that direct heating of the hypothalamus, via implanted thermodes, caused increased respiratory rate and vasodilatation even in a cold environment, while its direct cooling caused decreased respiratory rate and vasoconstriction even in a hot environment (Magoun et al., 1938; Beaton et al., 1941; Ström, 1950; Forster and Ferguson, 1952; Andersson et al., 1956; Andersson and Persson, 1957; Freeman and Davis, 1959; Hammel et al., 1960; Findlay and Ingram, 1961; Ingram and Whittow, 1961, 1962a,b, 1963; Andersson et al., 1962d; Nakayama et al., 1963; Hammel et al., 1963; Euler, 1964; Satinoff, 1964; Findlay and Whittow, 1966; Baldwin and Ingram, 1966, 1968; Whittow, 1968; Guieu and Hardy, 1970a; Gale et al., 1970; Mackrey and Bligh, 1971; Ingram and Legge, 1971; Kluger et al., 1973; Young et al., 1976). Support for the hypothesis that the preoptic/anterior hypothalamic area controls thermoregulation was provided by experiments in rats and rabbits in which lesions of this area destroyed the adaptive response to body cooling (Isenschmid and Schnitzler, 1914; Bazett and Penfield, 1922; Bazett et al., 1933; Pinkston et al., 1934; Frasier et al., 1936; Ranson and Ingram, 1935; Ranson et al., 1937; Clark et al., 1939; Ranson, 1940).

Also, electrical stimulation of this area in the ox (Ingram and Whittow, 1962a) and goat (Andersson et al., 1956) caused increased panting and vasodilatation. Further, single unit activity studies have shown that some neurons (warm receptors) in this area increased their firing rates during direct increased hypothalamic temperature, and others (cold receptors) responded to direct decreased hypothalamic cooling (Freeman and Davis, 1959; Nakayama et al., 1963; Hardy et al., 1964; Wit and Wang, 1968; Nakayama and Hardy, 1969; Gale et al., 1970; Guieu and Hardy, 1970a,b; Hellon, 1970; Jacobson and Squires, 1970; Boulant and Bignall, 1973). In addition, Bligh (1957a, 1966), Hayward et al. (1966), Baker and Hayward (1968c), Hayward and Baker (1968b), and Gale et al. (1970) contend that since the blood conveys thermal information about the body core to the brain, the thermoregulation of this area is controlled by the cerebral blood temperature. This hypothesis is supported by investigations in the rabbit (Kahn, 1904), dog (Moorhouse, 1911), cat (Forster and Ferguson, 1952; Newman and Wolstencroft, 1960), and sheep (Bligh, 1963a,b; Baldwin and Yates, 1977) which demonstrated that heating or cooling the carotid blood supply to the brain would elicit the same thermoregulatory responses as seen under hyperthermic and hypothermic conditions, respectively.

Besides regulating brain temperature, the countercurrent heat exchange mechanism within the cavernous sinus may also influence endocrine functions of the hypothalamic-pituitary axis. Environmental temperature changes have been shown to alter the plasma levels of some hormones. For example, in the bovine, serum prolactin levels (Koprowski

and Tucker, 1973; Wettermann and Tucker, 1976) are directly proportional
to environmental temperature variations, while plasma progestins and
corticosteroid levels (Stott and Wiersma, 1973), are inversely propor-
tional to temperature changes. Roussel et al. (1977) believed that the
higher levels of progesterone in the bovine, during hot weather, was the
result of environmental temperature alone. In addition, there is evidence
that the temperature sensitive neurons in the preoptic/anterior hypo-
thalamic area exert some control over pituitary hormone release (D'Angelo,
1960; Andersson et al., 1963; Chowers et al., 1964, 1966; Sundsten and
Matheson, 1966; Gale et al., 1970; Proppe and Gale, 1970). For instance,
in the rat (Itoh, 1954), dog (Szczepanska-Sadowska, 1974), and pig
(Forsling et al., 1975), heating of the preoptic/anterior hypothalamic
area increased the release of antidiuretic hormone (ADH), while in the
monkey (Hayward and Baker, 1968a), cooling of this area caused an inhibi-
tion of ADH release and diuresis. Bader et al. (1952) and Bass and
Henschel (1956) attributed diuresis during cold exposure in humans to
inhibition of ADH release from the neurohypophysis. Cooling of the
anterior hypothalamus resulted in increased secretions of ACTH in the dog
(Chowers et al., 1964, 1966) and ox (Gale et al., 1970; Calvert et al.,
1972).

Factors Influencing TSH Secretion

The best known mechanism controlling the secretion of thyrotropin
(TSH) is the negative feedback mechanism involving circulating blood
levels of thyroid hormone (Turner and Bagnara, 1976). When there is a

metabolic need for thyroid hormone or when circulating levels of tetraiodothyronine (Thyroxine or T_4) and/or triiodothyronine (T_3) are low, the hypothalamus is stimulated to secrete thyrotrophic releasing hormone (TRH), which reaches the thyrotrophic cells within the anterior pituitary via the hypophyseoportal system and stimulates the release of TSH. Thyrotropin, in turn, reaches the thyroid gland and stimulates production, as well as, release of thyroid hormone (T_3 and T_4) into the blood. As the circulating levels of T_3 and T_4 increase, there is a feedback inhibition on TSH release. However, the following aspects of this mechanism has not been settled; 1) whether T_3 or T_4 is the inhibiting agent, 2) the exact method of this inhibition, and 3) the exact location of the inhibition. Radioactive T_3 and T_4 have been found to collect in both the paraventricular region of the hypothalamus, as well as, in the neuro- and adenohypophysis (Turner and Bagnara, 1976). Thus, at present, it can only be assumed that TSH secretion is regulated at both the pituitary and hypothalamic levels via this mechanism.

Several factors have been shown to modify the above secretion sequence. For example, physical and emotional stresses are known to depress secretion of TSH (Brown-Grant and Pethes, 1960; Falconer, 1967; Leppäluoto et al., 1974a; Hefco et al., 1975; Döhler et al., 1977a,b). However, the exact method by which this inhibition occurs is not fully known. There is evidence that adrenal corticotrophic hormone (ACTH) may be involved in this inhibition, since stress increases the anterior pituitary secretion of ACTH and the adrenal corticosteroids, especially cortisol, is known to inhibit thyroid activity (Brown-Grant and Pethes,

1960; MacFarlane, 1963).

Another factor influencing TSH secretion is environmental temperature. The secretion of thyroid hormone has been observed to increase and decrease in rats exposed to cold and hot environments, respectively (Brown-Grant, 1956; Hsieh et al., 1957; Johnson and Ragsdale, 1960; MacFarlane, 1963; Reichlin et al., 1972; Mueller et al., 1974). Although the exact mechanism by which environmental temperatures influence TSH secretion has not been fully elucidated, it is believed to occur via a nervous reflex through the hypothalamus, since local preoptic cooling or heating have been demonstrated to increase or decrease, respectively, the secretion of TSH in the rat (McClure and Reichlin, 1964; Reichlin, 1964; Leppäluoto et al., 1974a), goat (Andersson et al., 1962a,b,c, 1963), and baboon (Sundsten and Matheson, 1966; Gale et al., 1970). Andersson et al. (1963) hypothesized that the control of TSH secretion by the "Heat Loss Center" in the preoptic/anterior hypothalamic region is via "warm detectors" which exert a certain inhibitory tone, the strength of which seems to increase in proportion to the rise in the temperature of the center (i.e., in proportion to the degree of activation of the central "warm detectors") and that cooling this area proportionally decreases the inhibition. They also thought that probably other hormonal cold defense mechanisms are also inhibited in a similar manner. More recent evidence indicates that the response of the pituitary thyrotropic cells to cold stimuli may be mediated by the release of norepinephrine from α-adrenergic hypothalamic neurons, which activate release of TRH and this, in turn, stimulates secretion of TSH (Tuomisto et al., 1975; Krulich et al., 1977).

These studies showed that the cold-induced increase of TSH secretion in the rat could be prevented by either norepinephrine depletors or α-receptor blockade. The dopaminergic system may be inhibitory to TSH secretion; however, there were no significant changes in serum TSH levels following dopamine receptor blockade, and neither ℓ-dopa nor apomorphine had any inhibitory effect on the TSH response to TRH at doses that would inhibit the cold-response (Tuomisto et al., 1975; Krulich et al., 1977). It could be possible that the dopaminergic system is activated by increasing temperatures; however, this aspect has not been investigated.

MATERIALS AND METHODS

Surgical Procedures and Experimental Design

Ten Rambouillet ewes, aged one to three years, were used in this investigation (Table 2, p. 38). Seven days prior to experimentation, each animal was housed in an animal holding room, sheared, and accustomed to the handling necessary for the experimentation (i.e., room temperature, rectal temperature, heart rate, and respiratory rate were taken four times daily). During the course of the experiment, except for 24 hours prior to each surgical procedure, the animals were allowed free access to food and water.

After the animals were accustomed to handling, an indwelling venous catheter, used for withdrawing blood samples, was chronically implanted into the right external jugular vein of each ewe at approximately the level of the fourth cervical vertebra. The venous catheter consisted of a 61 cm long polyvinyl tubing (0.044" I.D.[1], 0.065" O.D.[2]) inserted through a silastic cannula (0.062" I.D., 0.125" O.D.), leaving 15 cm beyond each end of the silastic cannula. The silastic cannula eliminated kinking of the polyvinyl catheter, overcoming the impediment of blood withdrawal. A small knob of silastic cement, used for anchoring the catheter into the external jugular vein, was fashioned onto one end of the silastic cannula. The animal was anesthetized with fluothane

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[1] I.D. = Inner diameter.

[2] O.D. = Outer diameter.

(halothane, U.S P.) and the right external jugular vein was exposed by an 8.0 cm incision along the right jugular furrow, at the level of the fourth cervical vertebra. The venous catheter was filled with heparinized saline solution (400 units/ml) and then it was inserted into the external jugular vein, to the level of the silastic knob (approximately 15 cm), along the dorsal border of the vein. The catheter was held in place by passing 4-0 braided silk first through the adventitia of the jugular vein and surrounding fascia, and then through and around the silastic knob. The catheter was then exteriorized through a skin incision at the pre-scapular region and both incisions were closed with No. 1 surgical suture. An 18 gauge needle, fitted with luer-lock plug, was inserted into the exteriorized end of the catheter. Blood samples were withdrawn from the catheter by connecting a 10 ml syringe to the 18 gauge needle.

Three days post-jugular surgery, 10 ml blood samples and physiological data (i.e., room temperature, rectal temperature, heart rate, and respiratory rate) were obtained for the "Normal Phase," following the schedule in Table 1. The patency of the jugular catheter was maintained with heparin (10,000 units/ml) between samplings.

After the "Normal Phase" of blood samples was completed (Table 1), an upper respiratory bypass cannula (Figure 1) was chronically implanted into the trachea of each animal. The body (E) and cranial (C) and caudal (D) tubal extensions (modified for use in the sheep after Kluger and D'Alecy, 1975) were carved from a block of teflon. The inserts (A and B) were made of stainless steel and the cap (F) was made of plastic. The surgical technique for implantation of the upper respiratory bypass cannula was as follows:

Table 1. Schedule of blood sampling and physiological data[a]

Day of sampling	Time of day			
	8 a.m.	12 p.m.	4 p.m.	8 p.m.
1st	1[b]	1	1	1
2nd	1	1	1	1
3rd	1	1	1	1
4th	2	2	2	2
5th	2	2	2	2
6th	2	2	2	2
7th	2 (zero time bypass)	3	3	3
8th	3	3	3	3
9th	3	3	3	3
10th	3 (zero time post-bypass)	4	4	4
11th	4	4	4	4
12th	4	4	4	4
13th	4	-	-	-

[a]The physiological data of room temperature, rectal temperature, heart rate, and respiratory rate were recorded prior to each blood sampling.

[b]The numbers correspond to phases of experiment (i.e., 1 = normal, 2 = pre-bypass, 3 = bypass, and 4 = post-bypass).

1. Following anesthesia with fluothane and necessary preparations of the surgical field, the trachea was exposed approximately 4.0 cm caudal to the larynx by a 15 cm incision along the ventral midline of the neck.

Figure 1. Upper respiratory (tracheal) bypass cannula (modified from
Kluger and D'Alecy, 1975)

Solid arrows denote bypassed breathing with insert (A);
broken arrows denote normal breathing with insert (B).
(Manufactured by the work shop of the Engineering Research
Institute, Iowa State University, Ames, Iowa).

A - Bypass insert
B - Flow-through insert
C - Cranial tubal extension
D - Caudal tubal extension
E - Body
F - Cap
G - Leur lock needle with cap

F

G

B

A

E

B-LEVEL

C

D

A-LEVEL
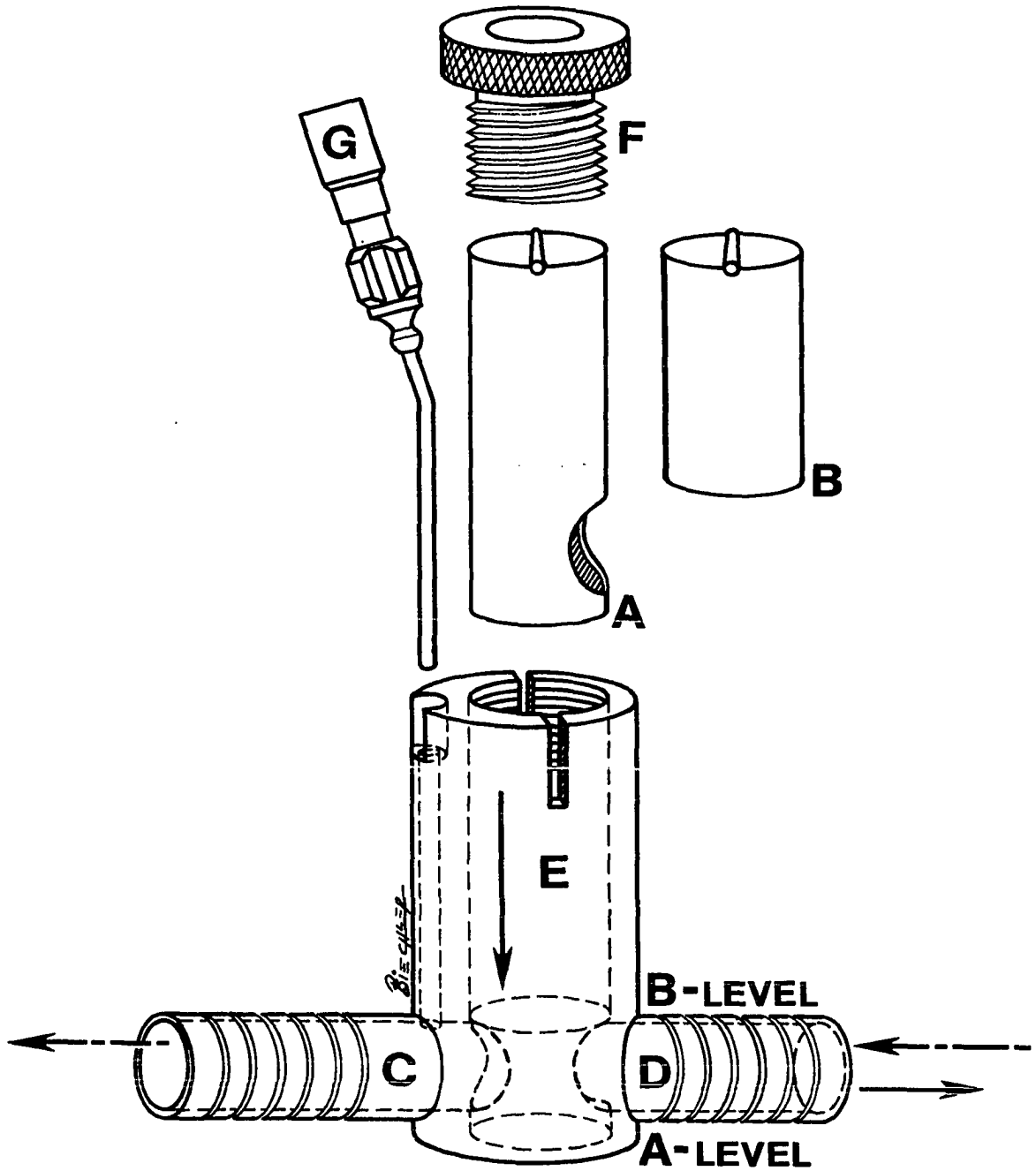
2. The tr.chea was transected and the cranial and caudal tubal extensions of the cannula were inserted into the trachea through the cut ends of the cranial and caudal segments, respectively, of the trachea. A double loop of No. 2 surgical silk was fastened around the trachea near each cut end, providing an airtight seal between the trachea and the tubal extensions of the cannula.

3. To prevent any possible slippage of the trachea from the tubal extensions of the cannula, supporting sutures were placed through the lateral sides of the trachea and the ends of the trachea were drawn towards the body of the cannula (Figure 2).

4. The surgical wound was then closed with No. 1 surgical silk, leaving the body of the cannula extending beyond the surface of the skin (Figure 3). At least once a day, the inserts (A or B, depending on the period of the experiment) were removed and the cannula cleaned of mucus.

Three days post-tracheal surgery, 10 ml blood samples and physiological data were obtained for the "Pre-Bypass Phase" following the schedule in Table 1. The "Bypass Phase" followed, beginning with the collection of a blood sample and recording of the physiological data designated "Zero Time Bypass" (Table 1). Immediately after the "Zero Time Bypass" data were collected, the flow-through insert (B) of the upper respiratory bypass cannula (Figure 1) was replaced by the bypass insert (A). Normal respired airflow through the nasal cavity was then interrupted. The animals remained on the bypass breathing for 72 hours, during which time blood samples and physiological data were obtained following the schedule in Table 1.

Figure 2.   Surgical implantation of the upper respiratory bypass
            cannula into the trachea of a sheep

            A - Upper respiratory bypass cannula
            B - Caudal end of trachea
            C - Cranial end of trachea
            D - Double loop of suture for airtight seal between
                trachea and cannula
            E - Supporting suture to prevent slippage of trachea
                from cannula

Figure 3.   Chronically implanted upper respiratory bypass cannula in
            situ

            A - Upper respiratory bypass cannula
            B - Interrupted cutaneous sutures
            C - Purse-string cutaneous sutures
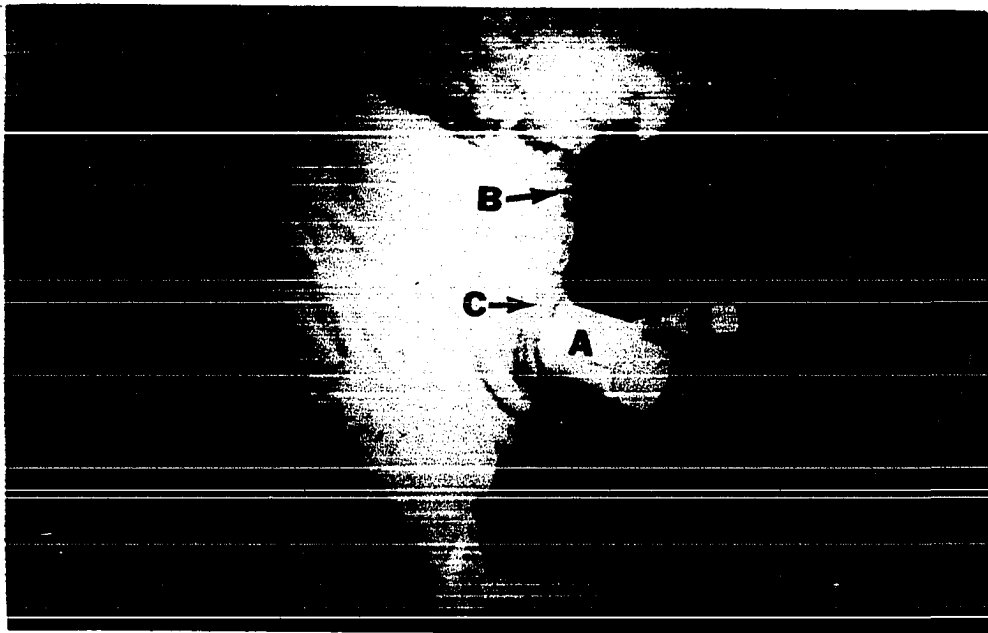
The animals wer: finally returned to normal nasal breathing, after the "Zero Time Post-Bypass" blood sample and physiological data were obtained (Table 1), by replacing the flow-through insert (B) into the upper respiratory bypass cannula (Figure 1). For the next 72 hours, blood samples and physiological data were obtained for the "Post-Bypass Phase," following the schedule in Table 1.

Thus, the experimental design of this investigation consisted of four periods of blood samplings and physiological data recordings:

1. Normal phase - to determine the normal serum levels of TSH in the sheep under investigation.

2. Pre-Bypass phase - to determine if surgical stress affected the serum levels of TSH.

3. Bypass phase - to determine if interruption in normal nasal breathing, which has been shown to increase brain temperature in sheep (Krabill, 1979), will affect the serum levels of TSH.

4. Post-Bypass phase - to determine if resumption of normal nasal breathing will restore the TSH levels of the "bypass phase" to "pre-bypass" levels.

All blood samples were stored at 4°C for 24 hours before serum was collected by centrifugation. The serum samples were then stored at -20°C until assayed for TSH content.

Pr)cedure for Radioimmunoassay of Ovine TSH

A. Preparation of Anti-Ovine TSH Serum:

    1. Reagents:

        a. Anti-Ovine TSH Serum[1]

        b. Phosphate buffered saline-Ethylenedinitrilotetraacetic

           acid (0.05M) solution (PBS-EDTA), pH 7.0--0.15M NaCl,

           C.01M sodium phosphate, with 0.01% thiomersol (or any

           antibacterial agent), EDTA.

        c. Normal rabbit serum (NRS)

        d. Ovine LH and FSH[2]

    2. Procedure:

        a. Full strength antiserum was diluted 1:400 in 0.05M PBS-

           EDTA, pH 7.0.

        b. NRS was also diluted to 1:400 in 0.05M PBS-EDTA, pH 7.0.

        c. Anti-ovine TSH serum was then taken to a working

           dilution of 1:100,000 using 1:400 NRS.

        d. After dilution to 1:100,000, the antiserum was pre-

           absorbed with ovine LH and FSH:

           i. added 50 ng of LH and 50 ng of FHS per ml of

               diluted antiserum.

           ii. Incubated for 24 hours at 4°C with stirring.

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[1]Provided by Dr. S. L. Davis, Department of Animal Industry, University of Idaho, Moscow, Idaho 83843.

[2]A gift from the National Institute of Arthritis, Metabolism and Digestive Diseases, a division of the National Institute of Health.

e. Appropriate aliquots (50-100ml) were then snap frozen in dry ice-2-methyl butane and stored at -20°C until use.

B. Preparation of Reference Standard Hormone:

   1. Reagents:

      a. NIH-TSH[1]

      b. PBS-1% Bovine Serum Albumin (BSA), pH 7.0.

   2. Procedure:

      a. Weighed approximately 50-100ug of NIH-TSH on a Cahn micro electro-balance.

      b. Dissolved in PBS-1%BSA to a concentration of 100ug/ml, then accurately diluted to 100ng/ml in PBS-1%BSA, pH 7.0.

      c. Aliquots (3.0ml) were quick frozen and stored at -20°C until use.

C. Preparation of Separation Column:

   1. Reagents:

      a. Small column (0.8 x 20cm).

      b. Biogel P-60 (100-200 mesh).

      c. PBS-1%BSA, pH 7.0.

   2. Procedure:

      a. Packed column with 12cm of Biogel P-60 in cold room (4°C).

      b. Rinsed thoroughly with PBS-1%BSA.

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[1]A gift from the National Institute of Arthritis, Metabolism, and Digestive Diseases, a division of the National Institute of Health.

D. Radioiodination of Purified Bovine TSH:

   1. Reagents:

      a. Purified Bovine TSH[1]

      b. Phosphate buffered saline (PBS), pH 7.5--0.15M NaCl, 0.01M sodium phosphate, with 0.01% thiomersol (or any antibacterial agent).

      c. 0.5M phosphate buffer (pH 7.5) -- one part potassium phosphate monobasic to nine parts sodium phosphate dibasic.

      d. 0.05M phosphate buffer (pH 7.5).

      e. Carrier free I-125.

      f. Chloramine T solution, pH 7.5--1ug/ul in 0.05M phosphate buffer.

      g. Sodium metabisulfite, pH 7.5--2.5ug/ul in 0.05M phosphate buffer.

      h. Transfer solution, pH 7.5--10mg potassium iodide/ml of 0.05M phosphate buffer containing 16% sucrose (w/v).

      i. Bovine serum.

      j. Rinse solution, pH 7.5--10mg potassium iodide/ml of 0.05M phosphate buffer containing 8% sucrose (w/v).

      k. The PBS and PBS-1% BSA were stored at 4°C until use. Snap frozen aliquots of 0.5M phosphate buffer, rinse

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[1]Provided by Dr. J. G. Pierce, Department of Biological Chemistry, U.C.L.A. School of Medicine, Los Angeles, California 90024.

solution and transfer solution were thawed for use on day of iodination. Chloramine T and sodium metabisulfite solutions were made fresh and used within 2-3 hours of scheduled iodination.

2. Procedure:

a. Added 25ul of 0.5M phosphate buffer (pH 7.5) to a 1 ml serum vial containing 2.5ug (lug/ul in PBS, pH 7.5) of purified bovine TSH and mixed.

b. Added 0.5mCi of carrier free I-125.

c. Added 15ul Chloramine T solution and agitated for 60 seconds.

d. Stopped reaction by addition of 50ul of sodium metabisulfite solution and mixed.

e. Added 100ul transfer solution, mixed and transferred contents of vial to the column of Biogel P-60.

f. Added 100ul of bovine serum to vial, mixed and transferred the contents to the column.

g. Added 70ul of rinse solution to the vial, mixed and transferred contents to the column.

h. Eluted column with 0.05M phosphate buffer, pH 7.5.

i. Collected 0.5ml fractions of elute into tubes containing 0.5ml of PBS-1%BSA, pH 7.0. The iodinated TSH was eluted in fractions 3-10 and free I-125 was eluted in fractions 11-20.

E. Assay (f Serum Samples:

    1. Reagents

        a. PBS-1%BSA, pH 7.0

        b. Reference Standard Hormone (NIH-TSH)

        c. Serum samples

        d. Anti-ovine TSH serum (1:100,000)

        e. Iodinated bovine TSH

        f. Antirabbit gamma globulin (second antibody)

        g. PBS, pH 7.0

        h. NRS (1:400)

    2. Procedure:

        a. Assays were conducted in 10 x 75mm glass disposable culture tubes.

        b. All reagents and assay tubes were kept on ice while setting up the assay.

        c. Reference standard TSH was serially diluted to the following concentrations/200ul: 20ng, 10ng, 5ng, 2.5ng, 1.25ng, 0.625ng, 0.3125ng, 0.15625ng, and 0.078125ng.

        d. 200ul of serially diluted reference standard TSH was added to the appropriate duplicate standard tubes. Duplicate zero tubes received 200ul of PBS-1%BSA, pH 7.0 only. Three duplicate nonspecific binding tubes received 200ul (20ng) of reference standard TSH.

e. 300ul of PBS-1%BSA was added to all standard zero, and nonspecific binding tubes.

f. 300ul of PBS-1%BSA was added to the remaining assay tubes and then 200ul of the experimental serum samples was added to these remaining assay tubes.

g. 200ul of anti-ovine TSH serum (1:100,000) was added to all tubes except the nonspecific binding tubes which received 200ul of 1:400 NRS instead.

h. All tubes were vortexed and incubated at 4°C for 24 hours.

i. 1-0ul of iodinated bovine TSH (approximately 45,000 cmp/100ul) was added to all tubes. Two total count tubes, containing only 100ul of iodinated bovine TSH were added to the end of each assay set of tubes.

j. All tubes were vortexed and incubated at 4°C for 24 hours.

k. 200ul of antirabbit gamma globulin (second antibody) was added to each tube, except total count tubes.

l. All tubes were vortexed and incubated at 4°C for 72 hours.

m. 2.5ml of PBS, pH 7.0 was added to all but total count tubes.

n. All tubes, except total count tubes, were centrifuged at 2500-3000 r.p.m. for 30 min. at 4°C.

     o. Supernatant was decanted in all but total count tubes.

     p. All tubes were counted in a Beckman, Biogamma II

        counting spectrometer.

F. Assay Specificity Tests:

  1. Reagents:

     a. PBS-1%BSA, pH 7.0

     b. Reference Standard Hormone (NIH-TSH)

     c. Hypophysectomized Sheep Serum[1]

     d. Anti-ovine TSH serum (1:100,000)

     e. Iodinated bovine TSH

     f. Antirabbit gamma globulin

     g. PBS, pH 7.0

     h. NRS (1:400)

     i. An experimental serum sample whose TSH level has

        already been determined.

  2. Procedure:

     a. A duplicate set of standard, zero, and nonspecific

        binding tubes was set up, as for the regular assay

        (steps a through e of Procedures under Assay of Serum

        Samples)

     b. To a set of 10 duplicate (20 tubes) recovery tubes,

        200ul of serially diluted standard TSH (20ng-0.078125ng)

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[1]Provided by Dr. C. Kaltenbach, Department of Animal Science, University of Wyoming, Box 3354 University Station, Laramie, Wyoming 82070.

was then added to respective tubes. The duplicate zero
tubes of this set received 200ul of PBS-1%BSA instead of
standard hormone.

c. 200ul of hypophysectomized sheep serum was then added to
each recovery tube. This was followed with the addition
of 100ul of PBS-1%BSA to each recovery tube.

d. To a set of 5 duplicate (10 tubes) parallel tubes, the
following amounts of PBS-1%BSA were added to respective
pairs: 200ul, 300ul, 400ul, 450ul, 500ul.

e. To this set of parallel tubes, the following amounts of
an experimental serum sample were added to respective
tubes: 300ul, 200ul, 100ul, 50ul, 0ul (The volume in
each parallel tube was now 500ul).

f. The remainder of the procedure for all tubes of the
Assay Specificity Test (viz., Standard, Zero, Nonspecific
binding, Recovery, and Parallel tubes) was the same as
steps g through p of Procedures under Assay of Serum
Samples.

RESULTS

The experiment consisted of recording the physiological data of room temperature (RmT), rectal temperature (RT), respiratory rate (RR), heart rate (HR), and the collection of 10 ml blood samples for radioimmunoassay (RIA) of serum levels of TSH from 10 Rambouillet ewes during four different phases: Phase 1 (Normal Phase) represented data collected from the animals before tracheal surgery; Phase 2 (Pre-Bypass Phase) represented data collected after tracheal surgery but before normal nasal breathing was interrupted; Phase 3 (Bypass Phase) represented data collected during interruption of normal nasal breathing (animals were placed on bypass); and Phase 4 (Post-Bypass Phase) represented data collected after the animals were returned to normal nasal breathing.

The recorded physiological data (RmT, RT, RR, HR) and serum levels of TSH for the entire experiment (i.e., during Phase 1,2,3,4) were statistically analyzed for variations:

a. between individual animals

b. between the four phases of the experiment

c. between the average of all data and times of sample collection (i.e., 8 a.m., 12 noon, 4 p.m., and 8 p.m.)

d. between the average of all data of the three phases of normal nasal breathing (Phases 1,2,4) and bypassed breathing (Phase 3) and times of sample collection (8 a.m., 12 noon, 4 p.m., and 8 p.m.)

e. between serum levels of TSH and all data.

Table 2 lis_s the averaged raw values of all data from each ewe compiled by time during the four phases of the experiment. Each value is the mean of three observations, except for Phase 2, which is the mean of four observations, due to the fact that Zero-time bypass (Table 1) was taken just prior to placing the animals on bypass breathing. Table 3 gives the total means of all data from Table 2 by time within the four phases of the experiment. Each value is the mean of 30 observations, except for Phase 2, which is the mean of 40 observations. The total phase means are listed at the bottom of the table. Figures 4 and 5 are histograms graphically depicting the TSH values presented in Table 3. Figure 4 demonstrates that the TSH serum levels between Phases 1 and 2 (3.26 and 3.25 ng/ml, respectively) were essentially the same. However, there was an increase in TSH levels during Phase 3 (3.36 ng/ml), which subsequently decreased during Phase 4 (3.19 ng/ml). When the three phases of normal nasal breathing (Phases 1, 2, and 4) were averaged together and compared against Phase 3, an increase of 0.13 ng/ml (4.02%) was observed in TSH serum levels when the animals were on bypassed breathing. Figure 5 demonstrates that the serum levels of TSH between Phases 1 and 2 did not change over the time of sampling. The serum levels of TSH during Phase 3 were observably higher than the other three phases at the 8 a.m. and 12 noon samplings, however, at the 4 p.m. and 8 p.m. samplings, the TSH serum levels during Phase 3 were approximately the same or slightly lower than the other three phases. When Phases 1, 2, and 4 were averaged together and compared against Phase 3, increases of 0.27 ng/ml (8.83%)

Table 2. Mean data of ewes by time within phases of experiment

Sheep number	Age (years)	8 a.m.					Phase 1: NORMAL 12 noon				
		RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
51	1	23.3	118.0	102.8	60.0	2.30	32.7	120.0	102.4	61.0	2.72
53	1	24.0	126.7	103.0	59.7	2.42	22.0	105.3	102.9	60.7	2.50
75	2	24.7	90.7	103.0	61.0	4.28	26.0	93.3	104.7	61.0	4.15
76	3	32.7	97.3	102.4	57.7	3.28	40.3	102.0	104.0	59.0	3.37
105	1	22.0	98.0	101.4	58.0	3.90	22.7	79.3	101.6	59.7	3.70
113	2	32.0	82.7	102.1	61.0	3.13	52.0	82.7	102.8	61.0	3.05
146	1	24.0	110.0	102.0	60.0	2.62	25.3	115.3	102.7	61.0	2.78
150	2	24.0	88.7	103.2	57.7	3.47	26.0	86.0	104.1	59.0	3.38
185	1	21.3	136.7	104.2	59.7	2.98	31.3	144.0	104.6	60.7	3.23
197	1	26.0	132.7	103.5	60.0	2.63	26.0	133.3	103.2	61.0	3.58

		4 p.m.					8 p.m.		
RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
30.0	114.7	102.0	61.0	2.67	30.0	112.0	102.9	61.0	2.75
21.3	117.3	103.2	61.3	3.27	20.7	108.7	103.8	61.3	2.80
24.0	86.7	103.0	61.7	5.27	24.7	99.3	103.0	61.7	4.60
39.3	94.0	103.9	60.3	3.02	38.0	86.0	103.5	61.0	3.17
25.3	92.7	101.7	59.7	4.00	25.3	82.7	101.6	59.7	4.07
25.3	86.7	102.0	61.7	3.20	36.0	91.3	102.7	61.7	3.22
20.7	100.0	103.0	61.0	2.67	23.3	112.7	103.4	61.0	2.83
28.0	92.0	104.7	60.3	3.07	28.7	87.3	105.1	61.0	2.58
20.7	126.7	102.8	61.3	3.38	21.3	128.7	104.3	61.3	3.38
25.3	128.0	103.9	61.0	3.43	31.3	135.3	103.9	61.0	3.38

Table 2 (Continued)

Sheep number	Age (years)	8 a.m.					Phase 2: PRE-BYPASS 12 noon				
		RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
51	1	20.0	147.5	103.8	63.8	2.57	21.3	138.0	103.7	63.3	2.98
53	1	28.0	136.0	103.2	60.8	3.38	28.0	135.3	103.3	61.0	2.45
75	2	16.5	78.5	102.8	62.3	3.95	18.7	96.0	103.7	63.7	4.10
76	3	26.5	79.5	103.8	63.3	2.93	24.0	84.0	103.8	63.0	3.27
105	1	26.0	107.5	104.4	63.5	3.48	24.0	99.3	104.6	66.3	4.52
113	2	19.0	86.5	103.2	62.3	3.05	20.6	92.7	103.0	63.7	2.92
146	1	24.5	132.5	105.0	63.8	2.84	28.7	123.3	104.2	63.3	2.83
150	2	28.0	78.5	103.6	63.3	3.24	28.7	80.0	103.4	63.0	3.27
185	1	23.0	135.5	103.1	60.8	3.24	22.0	129.3	104.6	61.0	2.70
197	1	20.0	144.5	103.9	63.8	2.07	22.7	133.3	103.3	63.3	3.00

		4 p.m.					8 p.m.		
RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
22.7	138.7	103.1	64.3	3.02	21.3	140.0	103.3	63.3	3.23
25.3	132.7	103.7	62.7	3.45	25.3	125.3	103.9	62.7	3.57
18.0	92.7	103.4	64.3	4.23	20.0	99.3	104.7	66.3	4.15
24.7	80.7	103.4	62.7	3.07	22.7	85.3	103.6	62.7	3.75
27.3	104.0	104.7	68.0	4.80	28.7	100.7	104.8	68.0	4.20
20.7	88.0	102.6	64.3	3.17	28.0	100.0	103.2	66.3	3.12
23.3	112.0	104.1	64.3	2.53	21.3	117.3	103.3	63.3	3.12
22.7	76.7	103.1	62.7	3.25	28.0	86.7	103.0	62.7	3.30
24.7	137.3	104.2	62.7	3.58	26.0	144.7	104.4	62.7	3.22
21.3	132.0	103.4	64.3	2.63	22.7	132.7	104.5	63.3	2.34

Table 2   (Continued)

Sheep number	Age (years)	8 a.m.					Phase 3: BYPASS 12 noon				
		RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
51	1	14.7	150.3	102.8	61.0	2.45	19.3	140.7	103.9	65.3	2.55
53	1	17.3	144.7	103.7	58.7	2.80	20.7	131.3	104.1	58.7	2.52
75	2	16.0	93.3	101.8	61.7	3.92	70.0	94.7	102.7	64.0	4.42
76	3	18.7	109.3	104.2	58.0	4.00	18.0	97.7	104.0	57.7	4.55
105	1	22.0	87.3	103.0	64.0	4.52	20.7	104.0	103.0	66.7	3.75
113	2	18.0	78.7	101.7	61.7	3.15	20.0	93.3	102.0	64.0	3.48
146	1	18.0	139.3	103.7	61.0	3.02	32.0	129.3	104.4	65.3	2.85
150	2	25.3	72.0	102.9	58.0	3.50	25.3	71.3	102.8	57.6	3.32
185	1	16.7	142.7	102.3	58.7	3.47	19.3	121.3	103.5	58.7	3.48
197	1	16.7	154.0	104.0	61.0	2.89	20.0	143.3	103.3	65.3	4.02

		4 p.m.					8 p.m.		
RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
18.0	135.3	103.0	67.0	2.58	15.3	139.3	103.2	66.0	2.62
17.3	134.7	103.3	58.7	3.95	17.3	134.0	104.4	58.7	2.62
60.7	93.3	102.8	64.7	3.92	16.7	94.0	103.3	65.3	4.28
19.3	101.3	104.4	59.7	3.17	17.3	101.3	103.9	60.0	2.70
16.7	89.3	102.3	66.7	2.83	19.3	86.7	102.1	66.0	3.58
20.7	92.7	101.8	64.7	3.37	33.3	98.0	102.7	65.3	3.25
20.7	128.0	103.8	67.0	3.30	24.7	138.7	103.6	66.0	3.02
21.3	91.3	102.6	59.7	3.30	20.0	92.0	103.2	60.0	3.30
14.0	128.7	101.8	58.7	3.17	18.7	128.0	102.9	58.7	3.85
18.7	146.0	102.9	67.0	3.63	18.7	144.7	102.7	66.0	3.42

Table 2   (Continued)

Sheep number	Age (years)	8 a.m.					Phase 4: POST-BYPASS 12 noon				
		RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
51	1	20.0	136.0	102.7	62.0	2.58	20.7	136.0	102.6	63.7	2.75
53	1	18.7	126.0	102.9	58.7	3.02	19.3	120.7	103.8	59.3	3.10
75	2	18.7	122.0	102.3	58.0	3.98	28.7	112.0	103.7	58.7	4.28
76	3	22.7	106.7	105.1	60.0	2.83	25.3	108.7	105.1	61.7	3.37
105	1	24.0	84.7	103.6	64.7	2.70	24.0	79.3	103.0	68.3	2.80
113	2	61.3	115.3	102.7	58.0	3.05	34.0	100.0	102.4	58.7	3.27
146	1	22.0	130.0	104.1	62.0	3.10	24.0	141.3	104.0	63.7	3.20
150	2	30.7	81.3	103.2	60.0	3.30	38.0	88.0	103.2	61.7	3.30
185	1	20.0	124.7	102.6	58.7	4.32	20.0	132.7	102.9	59.3	3.37
197	1	26.0	162.0	105.6	62.0	2.28	21.3	151.3	103.9	63.7	3.65

| | 4 p.m. | | | | | 8 p.m. | | | |
RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
19.3	136.0	102.7	63.7	2.75	20.7	138.7	102.9	64.3	2.75
19.3	120.7	103.3	59.3	2.92	19.3	124.0	103.2	60.3	3.33
20.7	116.7	102.5	58.7	4.40	17.3	106.0	102.7	59.7	4.22
27.3	104.7	104.8	62.0	3.12	28.0	108.7	105.0	64.3	2.73
24.0	84.7	103.8	67.7	2.80	30.0	85.3	103.7	67.7	3.27
37.3	93.3	102.3	58.7	3.00	32.7	97.3	102.4	59.7	3.12
22.7	132.7	103.4	63.7	2.82	22.7	140.0	104.1	64.3	3.07
30.7	91.3	102.6	62.0	3.25	40.0	86.0	103.3	64.3	2.87
19.3	125.3	102.3	59.3	3.60	23.3	128.0	103.2	60.3	3.75
22.7	146.7	104.7	63.7	2.90	21.3	153.3	104.2	64.3	2.85

Table 3. Total means grouped by time within phases of experiment

Time	Phase 1					Phase 2				
	RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
8 a.m.	25.4	108.1	102.8	59.5	3.10	23.2	112.7	103.7	62.7	3.07
12 noon	30.4	106.1	103.3	60.4	3.25	23.9	111.1	103.8	63.2	3.20
4 p.m.	26.0	103.9	103.0	60.9	3.40	23.1	109.5	103.6	64.0	3.37
8 p.m.	27.9	104.4	103.4	61.1	3.28	24.4	113.2	103.9	64.1	3.40
Total phase means	22.4	105.6	103.1	60.5	3.26	23.6	111.7	103.7	63.5	3.25

	Phase 3					Phase 4			
RR	HR	RT	RmT	TSH	RR	HR	RT	RmT	TSH
18.3	117.2	103.0	60.4	3.37	26.4	118.9	103.5	60.4	3.12
26.5	112.6	103.4	62.3	3.49	25.5	117.0	103.5	61.9	3.31
22.7	114.1	102.9	63.4	3.32	24.3	115.2	103.2	61.9	3.16
20.1	115.7	103.2	63.2	3.26	25.5	116.7	103.5	62.9	3.20
21.9	114.9	103.1	62.3	3.36	25.5	117.0	103.4	61.8	3.19

Figure 4. Histogram of serum TSH levels compared over phases of the experiment

The values over each bar represents the standard deviations.
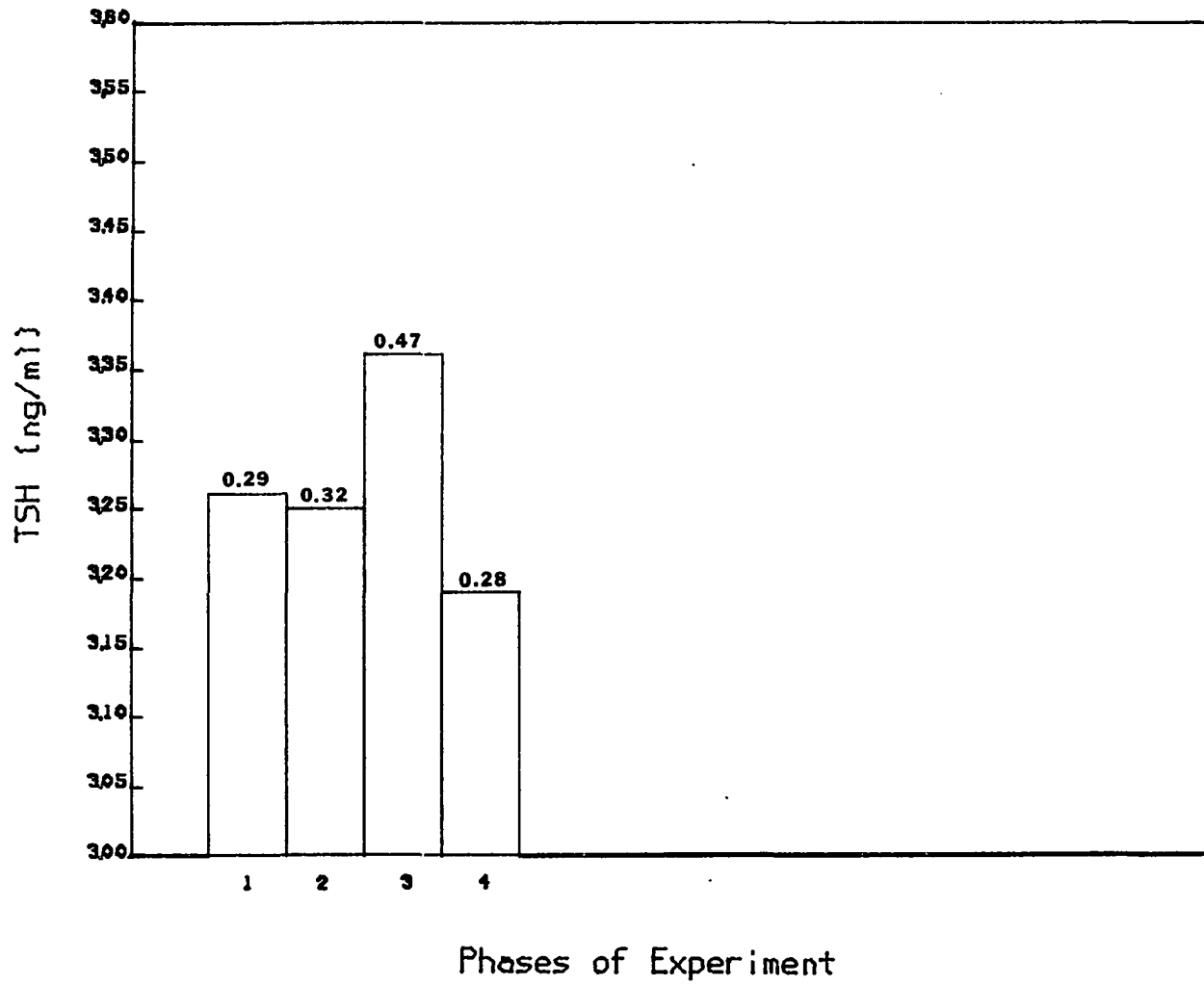
Figure 5. Histogram of serum TSH levels compared by phases over time of sampling Values over bars represents the standard deviations.
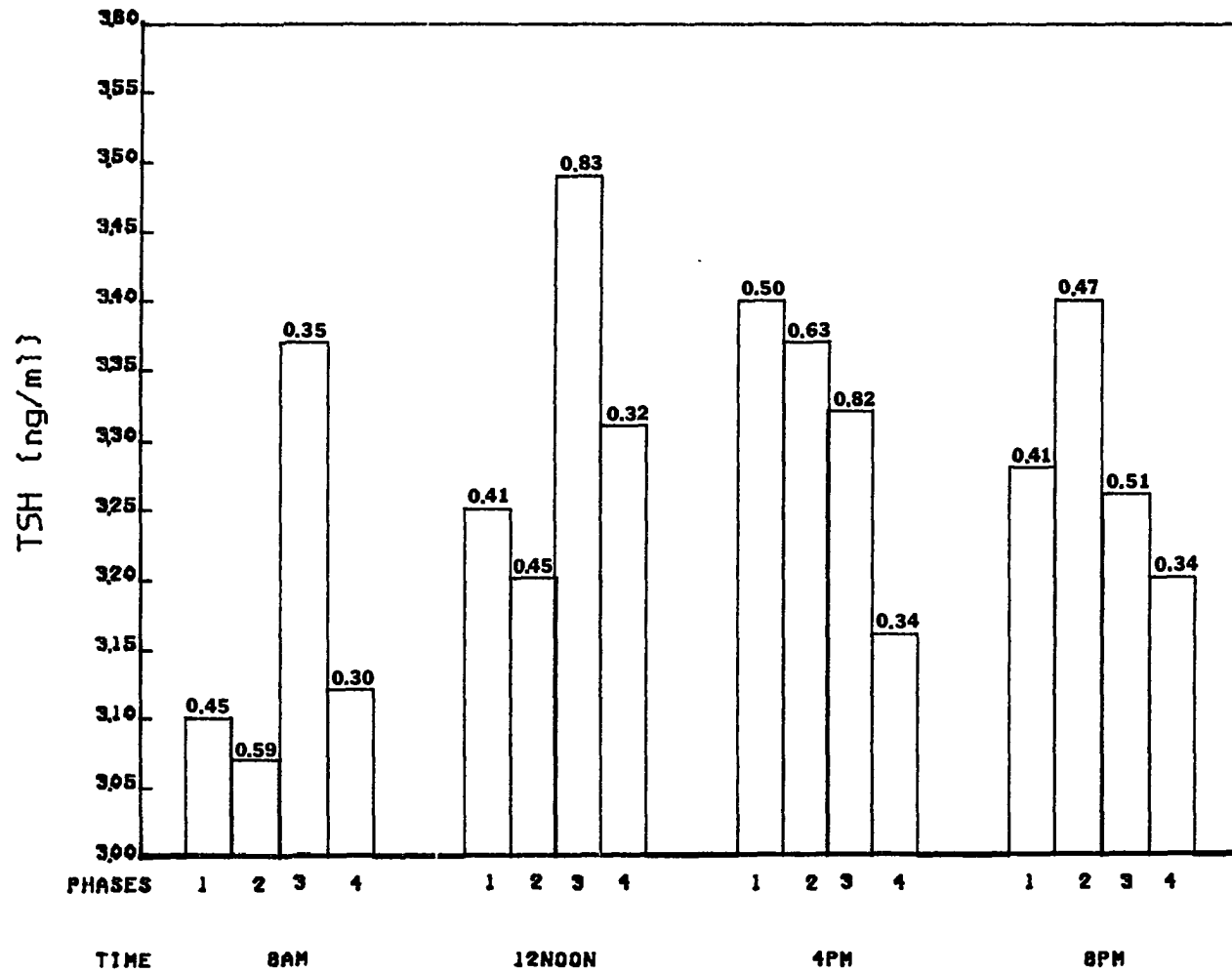
at 8 a.m., and o : 0.24 ng/ml (7.40%) at 12 noon were observed when the animals were on bypassed breathing.

Table 4 gives the F-values and probabilities from the analysis of variance (ANOVA) for the total means of all parameters, as listed in the last row of Table 3, when compared between individual sheep (SN) and between the four phases of the experiment (POE). There was a significant difference in heart rate and room temperature between sheep (PR>F = 0.001 and 0.02, respectively) and the phases of the experiment (PR>F = 0.03 and 0.01, respectively). The room temperature, averaged over the entire experiment, was 0.22°C higher during the bypassed phase as compared to the average of the three normal nasal breathing phases. Only at 8 a.m., the room temperature during the bypassed period was 0.28°C lower than during the three normal nasal breathing phases.

Table 5 highlights the F-values and probabilities from the analysis of variance (ANOVA) of the means of the experimental parameters during time as listed in Table 3, when compared between individual sheep (SN) and between phases of the experiment (POE). Respiratory rate was significantly different (PR>F = 0.06) between phases at 8 a.m. as well as it was highly significant between sheep (PR>F = 0.008) and the phases of experiment (PR>F = 0.005) at 8 p.m. Heart rate was significantly different between sheep during all time periods (PR>F = 0.0001) and it was significantly different between the phases of the experiment at 4 p.m. (PR>F = 0.03) and at 8 p.m. (PR>F = 0.008). Rectal temperature was significantly different between sheep at 8 a.m. (PR>F = 0.05) and 4 p.m. (PR>F = 0.04) and it was different between phases of the experiment at

Table 4. F-values and probabilities from the analysis of variance (ANOVA) of total means by phases (Table 3)

Method of analysis	Resp. rate		Heart rate		Rectal temp.		Room temp.		TSH	
	F	PR>F	F	PR>F	F	PR>F	F	PR>F	F	PR>F
SN	1.16	0.36	26.87	0.001	2.05	0.07	2.73	0.02	9.29	0.0001
POE	1.68	0.19	3.51	0.03	1.98	0.14	4.57	0.01	0.60	0.62

Table 5. F-values and probabilities from the analysis of variance (ANOVA) of total means by time (Table 3)

Time	Method of analysis	Resp. rate		Heart rate		Rectal temp.		Room temp.		TSH	
		F	PR>F	F	PR>F	F	PR>F	F	PR>F	F	PR>F
8 a.m.	SN	1.44	0.22	15.50	0.0001	2.24	0.05	2.28	0.05	6.41	0.0001
	POE	2.78	0.06	1.50	0.24	2.90	0.05	8.75	0.0003	1.22	0.32
12 noon	SN	0.83	0.60	20.63	0.0001	1.74	0.13	3.21	0.009	6.74	0.0001
	POE	0.76	0.52	2.22	0.11	0.76	0.53	3.23	0.04	1.19	0.33
4 p.m.	SN	0.69	0.71	20.09	0.0001	2.40	0.04	2.73	0.02	4.60	0.0009
	POE	0.32	0.81	3.42	0.03	1.79	0.17	4.45	0.01	0.60	0.62
8 p.m.	SN	3.29	0.008	26.13	0.0001	1.08	0.41	1.70	0.14	6.55	0.0001
	POE	5.45	0.005	4.81	0.008	1.24	0.31	3.38	0.03	0.56	0.64

8 a.m. (PR>F = 0.05). The rectal temperature, averaged over the entire experiment, was 0.16°C lower during the bypassed phase as compared to the average of the three phases of normal nasal breathing. Room temperature was significantly different (PR>F = 0.05, 0.009, and 0.02, respectively) between sheep at all time periods, except 8 p.m. and it was significantly different at all time periods during phases of the experiment (PR>F = 0.0003, 0.04, 0.01, and 0.03, respectively). The serum levels of TSH was significantly different only between sheep at all times of sampling (PR>F = 0.0001, 0.0001, 0.0009, and 0.0001, respectively).

Table 6 is the F-values and probabilities of the analysis of variance comparing the averaged data taken during three normal nasal breathing phases (Phases 1, 2, and 4) against the bypassed phase (Phase 3). It showed that only the respiratory rate was significantly different at 8 a.m. (PR>F = 0.002) and 8 p.m. (PR>F = 0.005). The serum levels of TSH approached significance at the 8 a.m. (PR>F = 0.10) and 12 noon (PR>F = 0.12) time periods, thus reflecting the differences observed in Figure 5 during the same time periods. However, a t-test of the hypothesis that there is a difference in the overall TSH serum levels between normal nasal breathing and bypassed breathing was not significant at the 95% confidence level.

Table 7 highlights the correlations between the serum levels of TSH and the other parameters for the entire experiment as well as during the four phases of the experiment. It showed that there was a significant but small negative correlation between TSH serum levels and heart rate, rectal temperature, and room temperature (i.e., as TSH serum levels

Table 6. F-values and probabilities from the analysis of variance comparing normal nasal breathing (Phases 1 + 2 + 4) vs. bypassed breathing (Phase 3)

Time	Resp. rate		Heart rate		Rectal temp.		Room temp.		TSH	
	F	PR>F	F	PR>F	F	PR>F	F	PR>F	F	PR>F
8 a.m.	18.00	0.002	0.97	0.35	3.12	0.11	1.13	0.32	3.40	0.10
12 noon	0.00	0.99	0.13	0.73	0.28	0.61	0.35	0.57	3.00	0.12
4 p.m.	0.14	0.72	4.95	0.05	3.80	0.08	1.37	0.27	0.00	0.95
8 p.m.	14.04	0.005	2.83	0.13	2.81	0.13	0.30	0.60	0.05	0.83

Table 7. Correlation of TSH serum levels with physiological data

Parameters	Total experiment		Phases of experiment							
			1		2		3		4	
			R	PR>R	R	PR>R	R	PR>R	R	PR>R
Resp. rate	0.01	0.80	-0.10	0.28	0.01	0.88	0.15	0.11	-0.10	0.27
Heart rate	-0.19	0.0001	-0.21	0.02	-0.25	0.004	-0.21	0.02	-0.06	0.48
Rect. temp.	-0.11	0.01	-0.16	0.08	0.06	0.51	-0.11	0.26	-0.26	0.0004
Room temp.	-0.09	0.05	-0.00	0.99	0.08	0.39	-0.11	0.22	-0.43	0.0001

TSH serum levels

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increased, these parameters decreased and conversely, as TSH serum levels decreased, these parameters increased). The significant but small negative correlation between TSH serum levels and heart rate was present during the first three phases of the experiment. The significant but small negative correlations between TSH serum levels and both rectal and room temperatures observed for the total experiment were due to the greater and highly significant negative values for these correlations during Phase 4.

Figure 6 presents graphs demonstrating that the serum levels of TSH over time varied during the four phases of the experiment. No consistent pattern was, however, observed.

Figure 6. Graphs of serum TSH levels over time of sampling with each phase of the experiment

(Normal Phase = Phase 1; Pre-bypass Phase = Phase 2; Bypass Phase = Phase 3; Post-Bypass Phase = Phase 4).
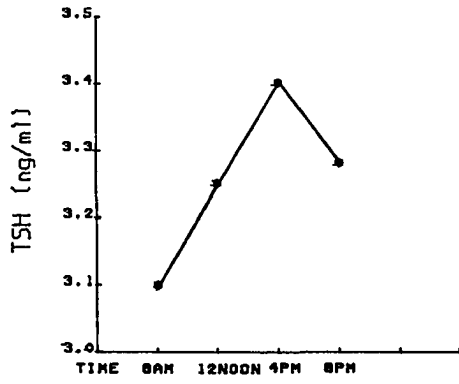
Normal Phase
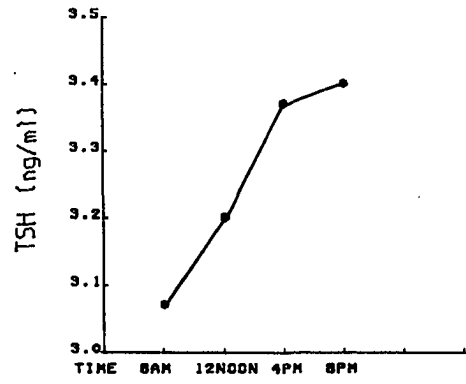
Pre-Bypass Phase
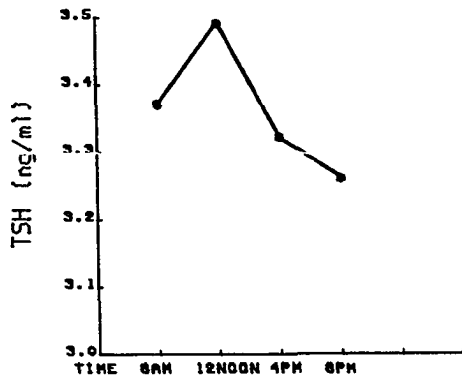
Bypass Phase
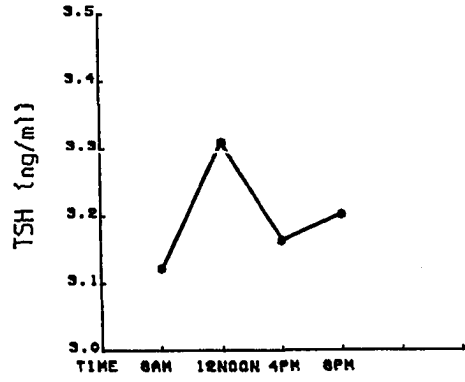
Post-Bypass Phase

DISCUSSION

Sheep were used in this investigation for the following reasons:

1. Although most mammals can regulate body temperature within 1°C (Scholander et al., 1950), the sheep has been found to be the most thermostable homeotherm (Graham et al., 1959; Bligh and Harthoorn, 1964, 1965; Hemingway et al., 1966), being able to survive in both hot and cold environments (Lee, 1950; Schmidt-Nielsen, 1964). Their successful survival in hot environment has been attributed to panting (Lee, 1950; Baker and Hayward, 1968a) and to the cooling of the brain via the carotid rete within the cavernous sinus. The latter allows a rise in body temperature without elevating the brain temperature above a critically damaging level (Baker and Hayward, 1968a; Young et al., 1976).

2. All the blood destined to supply the brain of the sheep first passes through the carotid rete (Baldwin and Bell, 1963; Baldwin, 1964; Baker and Hayward, 1968d; Baldwin and Yates, 1977) and is thus temperature conditioned. The basilar artery does not appear to contribute significantly to the formation of the cerebral circle (Circle of Willis) in the sheep and is considered to be a caudally directed branch of that circle (Daniel et al., 1953).

3. Hemingway et al. (1966) reported that the hypothalamus in the sheep is the coolest portion of the brain, because of its close proximity to the cerebral arterial circle which receives temperature conditioned blood from the carotid rete within the cavernous sinus. Thus, any change in the local hypothalamic temperature by reducing the

efficiency of the countercurrent "internal heat exchange system" in the cavernous sinus may affect pituitary hormone secretions, similar to those evoked by direct thermal stimulation of this area.

4. Previous work from the same laboratory (Krabill, 1979) demonstrated that hypothalamic temperature could be elevated as much as 1°C by interrupting the normal nasal breathing via an upper respiratory bypass cannula implanted chronically into the trachea of sheep. Krabill's work, in the sheep, substantiated the importance attached to "external and internal heat exchangers" expounded by Magilton and Swift (1967, 1968, 1969) for regulation of the canine brain temperature.

In this study, the thyroid stimulating hormone (TSH) was investigated for the following reasons:

1. It is an important regulator of metabolic heat production via its influence on thyroxine secretion from the thyroid gland (Turner and Bagnara, 1976).

2. Its rate of secretion in the rat, goat, and baboon is not only influenced by environmental temperatures, but also by direct local changes in hypothalamic temperatures (McClure and Reichlin, 1964; Gale et al., 1970; Leppäluoto et al., 1974a). In addition, Andersson et al. (1963) believed that the preoptic/anterior hypothalamic region controlled the TSH secretion in the rat by exerting an inhibitory tone which was proportional to the rise in temperature of the area. They believed that lowered hypothalamic temperatures proportionally decreased the inhibition.

3. Borger and Davis (1974) developed a radioimmunoassay (RIA) specifically for the ovine TSH which could provide an accurate assessment of TSH serum levels.

The premise of this investigation was based on the facts that:

1. There is a temperature differential of as much as 1°C between the cerebral and core blood in the relaxed, unanesthetized sheep, because of the countercurrent heat exchange between the carotid rete and the cooled venous blood in the cavernous sinus (Baker and Hayward, 1968d).

2. This temperature differential can be removed by interrupting the normal nasal breathing which reduced the effective cerebral cooling of the "internal heat exchanger" (Krabill, 1979).

3. Since TSH serum levels are influenced by hypothalamic temperatures, this increased hypothalamic temperature demonstrated by Krabill may affect the serum levels of TSH.

The following procedures were therefore followed in the experimental design, to minimize any factor, other than normal blood temperature, that may affect the secretion of TSH:

1. Each animal served as its own control and all experimental animals were treated alike as much as possible. However, individual variations, which were highly significant (PR > 0.0001) throughout the entire experiment, cannot be entirely eliminated. This factor can be minimized, however, by the experimental design which allows each animal to serve as its own control (Brown-Grant and Pethes, 1960), as well as, by treating all experimental units alike (Cochran and Cox, 1957). Thus, attempts were made, as much as possible, to treat all animals alike in

regard to handli..g, feed, water, housing, surgical procedures, and sampling intervals.

2. The seven day period used to accustom the animals to the handling necessary for the experiment was an attempt to reduce disturbance stress. However, this was not always successful. Stress of any kind is known to influence secretions of pituitary hormones (Brown-Grant and Pethes, 1960; Falconer, 1967; Leppäluoto et al., 1974a; Hefco et al., 1975; Döhler et al., 1977a,b). The animal room was also being used concurrently by two other researchers. Occasionally, while recording the physiological data, if someone walked into or a group of people walked by the room an increase in heart rate was noticed.

3. The external jugular catheter for withdrawing blood samples was designed to reduce the painful stress of jugular venipuncture as far as feasible, although it could be argued that the TSH serum levels of Phase 1 do not necessarily represent the true normal serum levels of TSH, because of the surgical stress inflicted by the implanted venous catheter. However, it was believed to be very minimal since the TSH serum levels of Phase 2 were not appreciably different from Phase 1 (Figure 4). The blood samples of Phase 2 were taken after chronic tracheal implantation of the bypass cannula, and it was considered a good indication that if this relatively more stressful tracheal surgery did not affect the TSH serum levels, the less stressful external jugular surgery would have very little influence.

The results of the experiment (Figure 4) showed a small increase (4.02%) in serum levels of TSH during the bypassed phase, as compared to

the other three normal nasal breathing phases. When the results are compared over time (Figure 5), this overall 4.02% increase, during Phase 3, was due largely to increases at 8 a.m. (8.83%) and at 12 noon (7.40%). At 4 p.m. and 8 p.m., the serum TSH levels were the same as and even slightly lower, respectively, than the other three phases. Although a t-test of the hypothesis that there is a difference in serum TSH levels between bypassed breathing (Phase 3) and normal nasal breathing (Phases 1, 2, and 4) was not significant at the 95% confidence level, Table 6 demonstrates that the increases at 8 a.m. and 12 noon almost approached a significance at the 90% and 88% confidence level, respectively. This nonsignificance could stem from the fact that the animals in this investigation were not sufficiently temperature-stressed, as experiments were conducted on resting, unanesthetized subjects. In most studies involving the effects of temperature on blood levels of endocrine hormones, especially TSH, extremes in temperatures were necessary to observe significant changes in hormone levels. For example, rats kept in a thermoneutral environment are usually placed in either an environment of 0°-5°C (MacFarlane, 1963; Leppäluoto et al., 1974a) or in an environment of 40°C (Mueller et al., 1974) to demonstrate significant increases or decreases, respectively, in serum TSH levels. In addition, Forsling et al. (1975) did not observe any change in plasma antidiuretic hormone (ADH) levels in the pig, until the rectal temperature was raised to 43°C. Baker et al. (1975) demonstrated that cold stimulation of nerve endings isolated from the bovine posterior pituitary gland caused release of vasopressin and oxytosin; however, the temperature of the medium in which the nerve endings were placed was kept at 0°C. Also,

in the goat, the preoptic region of the hypothalamus had to be cooled to 34°C (Andersson et al., 1962a,c, 1963) or heated to 41°C (Andersson et al., 1962b) before the appropriate TSH responses were evident. In the present experiment, although room temperature varied significantly between phases of the experiment (PR > F = 0.01), the maximum variation was not more than 1.70°C between phases. When the averaged room temperature of the three normal nasal breathing phases (Phases 1 + 2 + 4) are compared against the bypassed phase (Phase 3), the variation was only 0.22°C. Considering the 35-40°C changes in environmental temperature in the rat experiments, the room temperature changes in this experiment most probably did not represent a significant thermal threat to cause significant changes in serum TSH levels. A similar situation appears to exist concerning rectal temperature. In the ADH experiment in the pig (Forsling et al., 1975), a rectal temperature change of approximately 4°C was needed to cause significant changes in blood levels of ADH. Similarly, the hypothalamic temperature changes in the goat (Andersson et al., 1962a,b,c, 1963) necessary to cause changes in blood levels of TSH were approximately ± 4°C. In this experiment, rectal temperature only varied 0.16°C between the normal nasal breathing phases (Phases 1 + 2 + 4) and the bypassed phase (Phase 3). Although rectal temperature is not the most accurate indicator of brain temperature, it is a fairly reliable estimate of blood temperature when there is a sufficiently gradual change in climatic temperatures (Bligh, 1957b). Thus, the small variations in the rectal temperature in this investigation, reflected only small variations in blood temperature, which did not

represent a significant thermal change to cause significant variations in serum TSH levels. It is interesting to note that lowering the hypothalamic temperature 0.5°C in humans, as measured by tympanic membrane temperature, had no significant effect on radioimmunoassay of serum TSH levels (Berg et al., 1966). It thus appears that if temperature changes of either the environment or of the body are to significantly affect the serum levels of TSH, the changes have to be of a more significant magnitude than the changes present in this investigation.

Even though the small increase in serum TSH levels during Phase 3 was not statistically significant, this observation does merit discussion since a decrease, instead of an apparent increase, would be expected if, as Krabill (1979) demonstrated, the temperature around the hypothalamus increased during interruption of the normal nasal breathing. The following observations in this investigation were in agreement with similar observations stated in the literature:

1. There were significant negative correlations (Table 7) between serum TSH levels and rectal temperature (PR > R = 0.01) and room temperature (PR > R = 0.05), indicating that serum TSH levels were inversely related to environmental and rectal temperatures as stated in the literature for the rat and guinea pig (Cottle and Carlson, 1956; Woods and Carlson, 1956; D'Angelo, 1960; Heroux, 1960, Leppäluoto et al., 1974b). However, the increased serum levels of TSH during Phase 3 were not due to changes in room temperature in this experiment because the room temperature during this phase averaged 0.22°C higher than the room temperatures of the other three phases. Thus, if serum TSH levels were

inversely related to environmental temperature, then a decrease in TSH levels should have occurred during Phase 3 contrary to a modest increase as evidenced in this experiment. Minett and Sen (1945) concluded that the thermostability of the sheep is not influenced by small changes in ambient temperature and Bligh et al. (1965) attributed this to the insulating quality of the fleece. Since the sheep in this investigation were sheared, there is the possibility that room temperature could have influenced thermoregulation, however, Eyal (1963) found little difference in the thermoregulatory behavior of shorn and unshorn sheep.

2. During the bypassed phase, the rectal temperature averaged 0.16°C lower than the averaged rectal temperature of the other three phases. If, as stated above, the literature is correctly interpreted in that serum TSH levels are inversely related to rectal temperature, then the increased serum TSH levels observed during Phase 3 were related to the lower rectal temperature during this phase.

3. There was a monophasic variation in rectal temperature, in that it was lower at 8 a.m. (average of 39.6°C) than at 8 p.m. (average of 39.7°C), which has been previously reported in the sheep (Veeraraghavan and Mendel, 1963; Bligh et al., 1965). Holmes et al. (1960) reported that amongst several groups of sheep, the Rambouillet had the greatest monophasic variation in rectal temperature, averaging as much as 1.0° - 1.5°C. In the baboon (Sundsten and Matheson, 1966) and rhesus monkey (Hamilton, 1963; Hammel et al., 1963) this monophasic rectal temperature variation was reflected in similar variations in hypothalamic temperature. These investigators observed that hypothalamic temperature was lowest in the morning and highest in the evening. Hayward and Baker (1969)

attributed this .ooling of the hypothalamus at night during resting

periods to increased heat loss due to peripheral vasodilatation, together

with decreased heat production due to muscular inactivity, leading to

cooling of the core blood, body, and brain. They further believed that

during the course of the active day period, vasoconstriction and increased

muscular heat production increased core blood temperature and this, in

turn, gradually raised the hypothalamic temperature. This hypothesis is

in accord with the observations that in noncarotid rete homeotherms, the

temperature of the brain is influenced directly by the temperature of the

core blood perfusing it (Hayward et al., 1966; Hemingway et al., 1966;

Hunter and Adams, 1966; Hayward and Baker, 1969; Richards, 1970; Cabanac

and Caputa, 1979). This might explain the small increases in serum TSH

levels at 8 a.m. and 12 noon during Phase 3 of this experiment, as com-

pared to the other three phases (Figure 5). Since the temperature con-

ditioning system within the cavernous sinus became, seemingly, less

efficient because of interruption in normal nasal breathing (Krabill,

1979) during Phase 3 of this experiment, it is inferred from the above

observations that the hypothalamic temperature became directly influenced

by core temperature blood in these sheep during this phase. If the

temperature of this blood was reduced at night, as proposed by Hayward

and Baker (1969), it would cool the hypothalamus which would evoke an

increase in serum TSH levels during the morning hours. As the core

blood temperature increased towards evening, this would signal a

decrease, as was observed, in serum TSH levels. During the normal nasal

breathing phases (Phases 1, 2, and 4), the influence of these small

variations in core blood temperature was reduced by a functional "internal heat exchange system" within the cavernous sinus and thus the response of TSH to these temperature changes was also reduced.

4. Leppäluoto et al. (1974b) observed in the rat that there was a circadian fluctuation in serum TSH levels with increasing levels during the morning hours, reaching a peak between 11 a.m. and 2 p.m., and decreasing levels in the afternoon; the lowest levels occurring between 4 p.m. and 9 p.m. These observations of Leppäluoto et al. correlated inversely with the monophasic hypothalamic temperatures described in the literature (Hamilton, 1963; Sundsten and Matheson, 1966) and also were supported by the studies which demonstrated the inverse relationship between serum TSH levels with direct thermal stimulation of the preoptic/ anterior hypothalamic region (Andersson et al., 1962a,b, 1963; McClure and Reichlin, 1964; Reichlin, 1964; Leppäluoto et al., 1974a). During the bypassed phase of this experiment (Figure 6), a circadian pattern similar to that described by Leppäluoto et al. was observed in the serum TSH levels in the sheep. Although this observation cannot be equated to the activities of the two species, since it is generally accepted that rats are more active at night than during the day, it is possible to equate the similarities of the pattern of serum TSH levels during the bypassed phase in the sheep in this experiment and that observed in the rat to changes in body temperature which would affect hypothalamic temperature. It is possible that, in the rat, increases in serum TSH levels during the morning hours may be due to increased body heat loss brought about by inactivity of this small animal, as proposed by Hayward

and Baker (1969). As the body begins to warm, during the late afternoon due to increased heat production, TSH levels begin to decrease, reaching their lowest levels at night when body heat is highest because of increased nocturnal activity. In the sheep, the increased serum TSH levels during the morning hours could be due to increased body heat loss from inactivity during the night. However, because of the larger body size of the sheep, it may take until the afternoon to increase body temperature sufficiently to cause a decrease in serum TSH levels. The lowest serum TSH levels would occur late in the evening when body temperature was at its highest, and then start to decline again because of inactivity at night. Since this circadian pattern was more pronounced during the bypassed phase (Phase 3) of the experiment, it is suggested that interruption in normal nasal breathing by reducing the efficiency of the "internal heat exchanger," caused a carotid rete species to react to changes in body temperature similar to a noncarotid rete species.

Although it is possible that the increased serum TSH levels during the bypassed phase (Phase 3) of this experiment may have resulted from more direct stimulation via core blood temperature, which is considered to be cooler than brain temperature in all homeotherms at rest in a neutral environment (Baker and Hayward, 1967a,b), as was the conditions in this experiment, there are several other factors that may have caused this small increase:

1. This increase during the bypassed phase could have been due to emotional stress. When these animals were placed on bypassed breathing, they would not eat temporarily unless they became starved or unless another sheep, not on bypassed breathing, was present and eating. This

behavioral chang~ was attributed to a decreased sense of smell owing to the interrupted air flow in the nasal cavity. The emotional stress of loss of smell could have increased serum TSH levels during this phase. However, this would not account for the circadian fluctuations seen during Phase 3 unless one considered that the emotional stress was greater in the morning and decreased as the day progressed.

2. The increase may have been caused by stress related release of other pituitary hormones and/or neurohormones. Stress is known to accelerate adrenal corticotrophic hormone (ACTH) release. However, the increases observed in this experiment could not be due to increased ACTH secretion, since ACTH inhibits TSH secretion which would result in a decreased serum TSH level (Brown-Grant and Pethes, 1960; MacFarlane, 1963). However, there is a possibility that stress related release of norepinephrine from adenergic nerve fibers in the hypothalamus may be involved (Tuomisto et al., 1975; Krulich et al., 1977). But this is not known since norepinephrine levels were not investigated.

3. These increases could have been due to decreased feedback inhibition of thyroid hormone on TSH secretion (Turner and Bagnara, 1976). Since triiodothyronine (T_3) and tetraiodothyronine (T_4) were not assayed, it could only be speculated that this might have occurred either because of decreased thyroid hormone secretion or increased peripheral utilization during Phase 3, which could also have resulted from stress. However, one would have to consider again that the stress progressively decreased during the day to account for the circadian fluctuations in serum TSH levels observed during this phase.

4. The une.:pected increases noticed in this investigation, in light
of the work of Krabill (1979), may have been due to the time of sampling.
The increase in hypothalamic temperature, when the animals were placed
on bypassed breathing in Krabill's investigation, was greater in the
evening, at a time when the differences between brain and body tempera-
ture in animals with a functional carotid rete were at their peak, than
in the morning. In this experiment, the serum levels of TSH during the
evening (8 p.m.) were lower (approximately 1.0%) for the bypassed phase,
as compared to the normal nasal breathing phases. This would be in line
with the expected decrease caused by increased brain temperature because
of the interruption in normal nasal breathing, as observed by Krabill.
It could be possible that due to the heat loss during the inactive
nocturnal period, as proposed by Hayward and Baker (1969), the differ-
ences between brain and body temperatures were lowered and that this
cooling of the hypothalamus caused increased TSH levels in the morning,
which diminished as the body temperature increased during the active day
period in Phase 3. However, since hypothalamic temperature was not
recorded at the time of blood samplings, this possibility is just a
speculation. It would explain the similarities in the serum TSH
levels observed during the bypassed phase and the results of Leppäluoto
et al. (1974b) in the rat. It would also explain the unexpected increases
in light of the work of Krabill (1979). Further, it would show that
during bypassed breathing in this experiment, the brain temperature was
being more directly influenced by core blood temperature, as is normally
found in noncarotid rete species, including primates (Hayward et al.,

1966; Hemingway et al., 1966; Baker et al., 1974; Caputa et al., 1976a,b), than during normal nasal breathing due to the decreased temperature conditioning ability of both "internal and external heat exchangers."

This research was conducted for developing an animal model simulating physical conditions existing in monogolism (Down's Syndrome) and in people with tracheostomies due to laryngeal cancer. Some similarities were observed between these experimental animals and mongoloids:

1. Alamanova (1973) observed that the air flow through the nasal cavity was reduced, which could be due to the underdeveloped facial bones (Benda, 1946). As a result, for the most part, mongoloids are mouth breathers. This condition would compare favorably with the bypassed phase of sheep in this investigation, since mouth breathing in mongoloids would reduce the effective brain cooling mechanisms believed to occur via the nasal cavity in humans (Caputa and Cabanac, 1978; Cabanac and Caputa, 1979).

2. Benda and Bixby (1939) found the basal metabolic rate in mongoloids to be significantly low, indicating dysfunction of the thyroid endocrine system. Although this condition is probably related to the Trisomy 21 aberration in mongoloids, there is a possibility that it could be due to abnormal brain temperature affecting directly hypothalamic influence in the release of this hormone. However, more investigation is needed in this area owing to conflicting reports of hypothyroidism (Baxter et al., 1975) indicating reduced levels of TSH, no difference (Saxena and Pryles, 1965; Hillman, 1969), and increased levels of TSH in mongoloids (Murdoch et al., 1977). A similar situation may exist in

people with perm.nent tracheostomies; however, possible endocrine differ-
ences in these patients, compared to normal nasal breathers, have not yet
been investigated.

SUMMARY AND CONCLUSIONS

The results of this investigation demonstrated that when the normal brain temperature regulation mechanism i.e., countercurrent heat exchange between the carotid rete and the cavernous sinus is deranged by interrupting the normal nasal breathing in the sheep, there was a small increase in serum TSH levels. This increase was especially evident during the morning hours but decreased progressively towards evening. The increase was not attributed to room temperature since during the bypassed phase (Phase 3), the room temperature averaged 0.22°C higher than during the normal nasal breathing phases (Phases 1, 2, and 4). However, it may have been related to rectal temperature which decreased 0.16°C during the bypassed phase, as compared to the three normal nasal breathing phases. It also considered possible that this increase could have resulted from: 1) emotional stress due to temporary loss of smell during the bypassed phase, 2) stress related release of other hormones, and 3) decreased feedback inhibition of thyroid hormone because of stress. However, the trends in serum TSH levels during Phase 3, which followed similar trends presented in the literature in noncarotid rete species, suggested that the increase was caused by direct stimulation of cooler core blood in the bypassed animal, than in the normal nasal breathing animal. This has been shown to be due to a lowered body temperature during the morning hours of the day, which has been hypothesized to be caused by loss of heat during a nocturnal inactive period (Hayward and Baker, 1969). Since this appears to be opposite to the results obtained by Krabill (1979), it is suggested that the experiment be repeated, adding recordings of

hypothalamic temperature during time of blood samplings to test whether the circadian fluctuations in TSH serum levels observed during bypassed breathing in this investigation are due to similar fluctuations in hypothalamic temperature caused by a general body cooling at night, which subsequently increases during the day as suggested by Hayward and Baker (1969).

Although a small increase in serum TSH levels was observed during the bypassed phase, this increase was not statistically significant at the 95% confidence level. Since in most studies involving the effects of temperature on blood levels of TSH extremes in temperature are necessary to elicit the appropriate response of TSH, it was considered that, in this experiment, the 0.22°C change in room temperature and the 0.16°C change in body temperature observed between the bypassed phase and the three normal nasal breathing phases did not represent a significant thermal change to significantly alter serum TSH levels. Thus, this insignificant temperature change was probably the cause of the nonsignificant change in serum TSH levels. It is suggested that this aspect be investigated by subjecting these animals to more stressful environmental conditions.

It is, therefore, concluded that the results suggest interruption in normal nasal breathing, by decreasing the efficacy of the "internal heat exchanger" within the cavernous sinus, causes the sheep, a carotid rete species, to react to changes in body temperature similar to a non-carotid rete species. This gives support to the possibility that these bypassed animals may be a useful model simulating physical conditions in humans. However, further investigation is needed.

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