Hormonal and Nervous Factors in the Regulation of the Body Temperature[1]

By G. MANSFELD[2], Budapest

(Concluded)

Naturally the question may be raised whether the thermoregulatory action of thermothyrin is of major physiological importance. That this is the case is well demonstrated by experiments performed in my laboratory by B. BERDE[3].

Pairs of guinea pigs of equal heat tolerance were chosen, and one of them was thyroidectomized. If thermothyrin production were of only secondary importance in thermoregulation, a thyroidectomized animal with its reduced rate of metabolism ought to tolerate a hot environment better than the control. Results were absolutely convincing: the reverse is the case (see Fig. 3). Thyroidectomy reduces heat tolerance very markedly. The only explanation forthcoming is that in the absence of the thyroid no thermothyrin A is available to reduce the rate of metabolism in a hot environment.

A review of the data furnished so far throws a beam of light in addition on the mechanism at the bottom of the observation of PLAUT and WILBRAND[4], termed by them "secondary chemical thermoregulation". The explanation of the fact that the heat production of animals, returned after exposure to heat to an environment of normal temperature, remains for hours below the basal level observed prior to exposure to heat, seems evident enough.

I believe there is no need for further evidence to convince us that the central nervous system is not the only factor responsible for thermoregulation, and that a very important part is played by chemical agents, by hormones. Many interesting aspects of physiological importance necessarily must remain undiscussed, and time permits only to mention the significance of hormonal thermoregulation in the great individual variation of heat and cold tolerance, the protective regulation offered by them during sleep, etc.

At this stage of our investigation came the remarkable discovery of THAUER[5] and of POPOFF[6]. It naturally interested me immensely, because it seemed to furnish additional evidence for the importance of hormonal thermoregulation.

Our earlier concepts of the problem can be condensed for the sake of brevity as follows:— Section of the cervical spinal cord is associated with loss of both physical and chemical thermoregulation; section of the *dorsal* medulla leads only to loss of physical regulation, while chemical regulation—the ability to increase oxidation in the cold—persists. The first question necessarily concerns the nervous pathways connect-

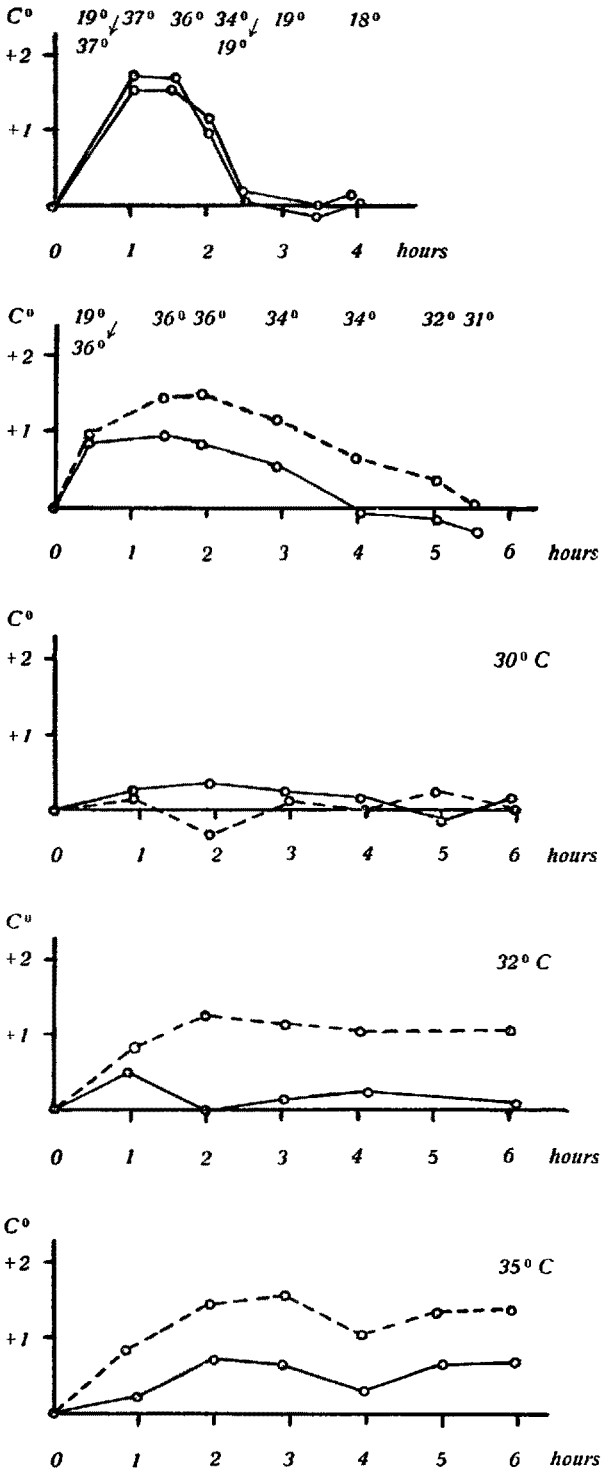

Fig. 3. —— = normal
--- = thyroidectomized

[1] A lecture.
[2] Institute of Physiology, University of Budapest.
[3] B. BERDE, Exper. *2*, 498 (1946).
[4] R. PLAUT and P. WILBRAND, Z. Biol. *74*, 191 (1922).
[5] R. THAUER, Pflügers Arch. *236*, 102 (1935).
[6] N. F. POPOFF, Pflügers Arch. *234*, 137 (1934).

ing thermoregulatory centre and periphery. Already CLAUDE BERNARD[1] attributed the caloric action to sympathetic nerves emerging below C_7. UNDERHILL and PACK[2] shared the same view, according to which impulses resulting in chemical thermoregulation would be transmitted through the lower cervical and stellar ganglia. This pathway is severed by transsection at the level of C_7, but remains intact if D_1 is transsected.

The discovery of THAUER and POPOFF affected my earlier work in two aspects. One of these is hormonal thermoregulation. The possibility had to be considered whether a regulating centre is really indispensable for the production of the heating hormone, or whether low external temperature has a direct effect on the thyroid.

The other factor was that the work of THAUER and POPOFF seemed to furnish additional evidence for my old and very much debated contention that sympathetic nerves convey impulses to resting muscle, which raise oxidation and so are responsible for the maintenance of a *chemical muscle tonus*[3].

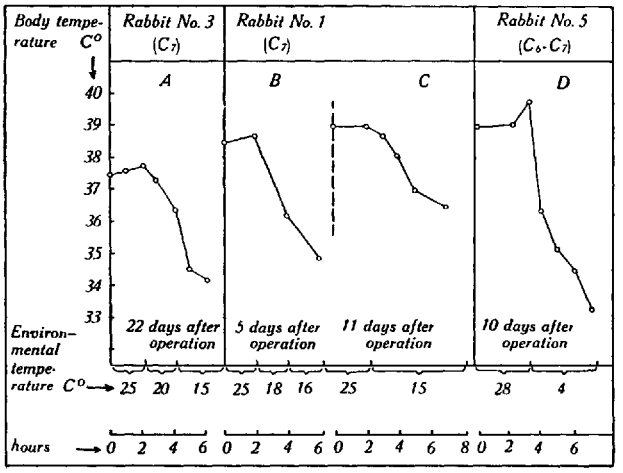

Fig. 4.

These considerations incited me to an immediate investigation of this problem[4]. Experiments on rabbits confirmed the basic fact observed by THAUER and POPOFF without a shred of doubt: 5–6 days after *cervical* section of the spinal cord some degree of thermoregulation evidently exists.

The animals maintain their body temperature in a room of average temperature. The next figure demonstrates the temperatures of rabbits some days after *dorsal* section of the spinal cord, under similar experimental conditions.

It is evident that the difference in the behavior following cervical and dorsal transsection is—in accordance with THAUER's statement—only a quantitative one. In both cases thermoregulation is very defective, and external temperatures easily tolerated by the intact animal are followed by a fall of body temperature.

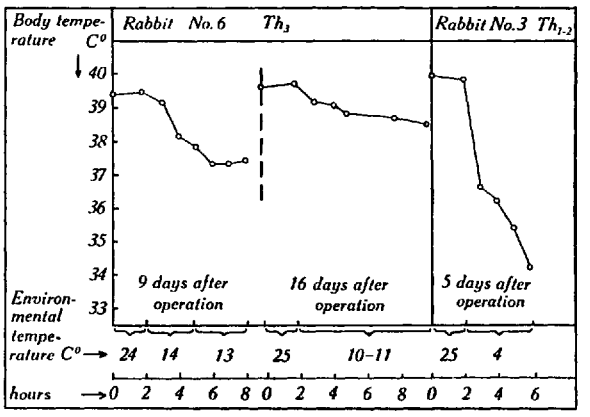

Fig. 5.

Looking for an explanation of this regained and, though deficient, nevertheless undeniable thermoregulation, two known experimental facts had to be considered. (1) POPOFF confirmed recently the observation of GOLTZ and EWALD[1], that vessels of the skin regain their tonus some time after transsection of the medulla was performed. (2) GRAFE[2] pointed out

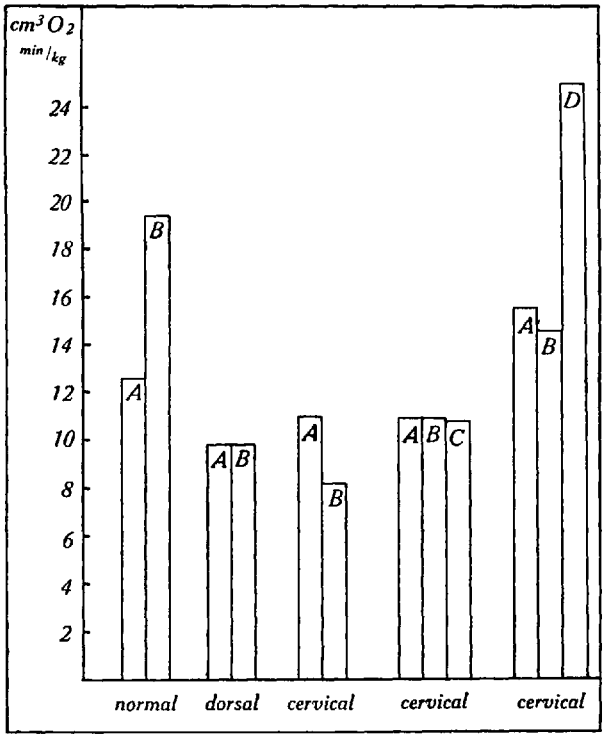

Fig. 6. *A* = at normal temperature
B and *C* = cooling lower half of the body
D = cooling proximal half of the body

[1] CL. BERNARD, Leçons de pathologie expériment. Paris 1871.
[2] FR. P. UNDERHILL and G. F. PACK, Am. J. Physiol. *66*, 519 (1923).
[3] G. MANSFELD and A. LUKÁCS, Pflügers Arch. *161*, 467 (1915).
[4] G. MANSFELD and ESZTER MÉSZÁROS, Arch. exp. Path. u. Pharm. *196*, 609 (1940).

[1] G. F. GOLTZ and I. R. EWALD, Pflügers Arch. *63*, 362 (1896).
[2] E. GRAFE in: Oppenheimers Hb. der Bioch. II. Edition, Vol. IX, pag. 42 (1924).

that cervical section of the spinal cord leaves one fourth part of the musculature, the muscles of the head and neck in unimpaired contact with the centre, therefore it can be understood easily that cooling of the whole animal is followed by increased heat production; a fact confirmed also by ISSEKUTZ, jun.[1].

Regained tonus of skin vessels is certainly a factor in controlling loss of heat, but may be passed over, being from our point of view of minor importance. The question of primary interest for us being whether the thermoregulation observed in the THAUER-POPOFF experiments is of central or peripheral origin, *we had to see what happens if exclusively those parts of the body are cooled that are severed from the centre.*

We measured therefore in a series of experiments the O_2-consumption of rabbits and dogs on which earlier a cervical or dorsal transsection of the spinal cord had been performed, before and after cooling the lower half of the body. The following two figures demonstrate the results.

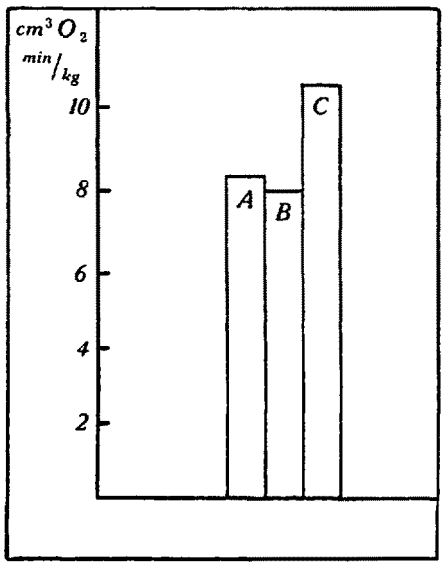

Fig. 7. *A* = at normal temperature
B = cooling lower half of the body
C = cooling proximal half of the body

The results are clear: cooling of the lower half of the body has no effect on O_2-consumption, neither in animals with cervical nor—and this is remarkable—in animals with dorsal transsection of the spinal cord, while cooling of the proximal half was followed by an immediate rise of heat production. The cooling of the distal parts was undertaken by packing them from all sides in rubber bags containing water of 8 C°, while the proximal half approximately to the level of the diaphragm was placed in a box of 28 C°, a fact of some importance later on.

The fact that no thermoregulatory response could be elicited by cooling the lower parts in animals with dorsal section is somewhat at variance with the old doctrine that dorsal section leaves chemical regulation intact. But more of this later.

At this stage of our investigation the simple routine of my laboratory to measure O_2-consumption after a 12–24 hour period of starvation revealed an unexpected startling fact. If rabbits on which cervical transsection was performed are fasted for 24 hours, the thermoregulation described by THAUER and POPOFF disappears completely, and in a room of 23 C° the body temperature declines rapidly to the fatal level of 28 C°. In animals with dorsal section of the spinal cord no such effect was observed; the animals maintain their body temperature after starvation within the same limits as without fasting (see Fig. 8).

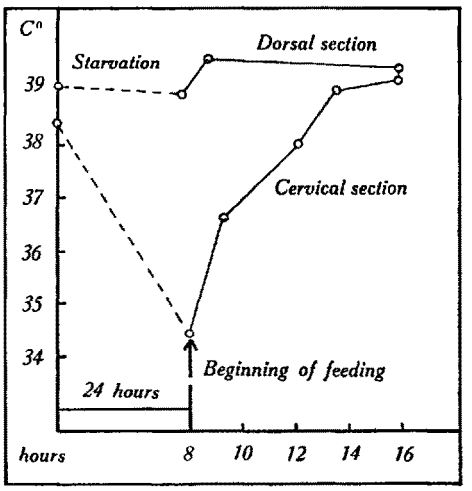

Fig. 8.

These rather startling observations demanded clarification. A number of possibilities had to be considered, and many approaches were thought of, when a simple observation carried us a good deal further. Animals with cervical section being most sensitive to changes of temperature were kept permanently in the laboratory under our own supervision, and so we noticed that they were exceedingly voracious. They simply devoured food placed before them and consumed often 80–100 g oats within half an hour. THAUER, without recording similar observations, mentions that 5 of his 9 animals died of gastric perforation—yet without ulceration; evidently in his cases a similar rupture of the stomach had occured such as we observed in two animals before we started to feed them in frequent intervals. Despite this voracity the animals loose weight constantly, as described by THAUER,and confirmed by ourselves. The preliminary conclusion seemed therefore warranted that all food ingested—however much it may be—is immediately metabolized.

Our next step was therefore to compare the O_2-consumption of animals with cervical and dorsal section of the spinal cord respectively in a well-fed state and after a period of starvation.

[1] B. ISSEKUTZ, jun., Pflügers Arch. *238*, 787 (1937).

Table X
The effect of starvation on the O_2-consumption

Duration of starvation in hours	O_2-consumption (mm^3 per kg and minute) starving	fed	Difference %
A. Normal rabbits			
24	8·9	9·4	+ 6
24	7·2	7·7	+ 7
24	11·2	12·1	+ 8
B. Rabbits with dorsal section of the spinal cord			
27	10·8	10·0	− 8
26	13·0	13·8	+ 6
24	9·8	9·4	− 4
24	11·0	11·7	+ 6
24	10·2	9·9	− 3
C. Rabbits with cervical section of the spinal cord			
13	6·9	11·1	+60
14	7·9	10·9	+38
20	9·1	15·4	+69
24	10·8	16·1	+49
26	8·7	12·5	+43

The results are clear-cut: not the figures for starved animals are below normal level, but the values for well-fed animals are excessively high. This means in other words that all foodstuffs are metabolized, and *the animal has lost its capacity for storage.* The mechanism that links loss and production of heat has broken down, the regulation between ventilation and the height of the gas flame has ceased to work, the body cut off from the regulating centre can be best compared to a room in which an adequate temperature may be maintained by an excessive quantity of fuel, although the loss of heat through ventilation is abnormal.

Yet another problem presents itself. Animals with dorsal transsection of the spinal cord also loose their capacity for thermoregulation, but nevertheless maintain their body temperature even after a period of starvation.

FREUND and GRAFE[1], and more recently OBERDISSE[2], found after dorsal section of the spinal cord a very high rate of O_2-consumption and concluded that chemical thermoregulation is not interfered with. Our experiments just mentioned prove this conclusion to be erroneous; the observation itself is nevertheless noteworthy. We endeavoured to clear up our problem by the following experiments: the O_2-consumption of rabbits was measured repeatedly under standardized conditions, then cervical or dorsal section of the spinal cord was performed, and the O_2-consumption was measured consecutively under exactly similar conditions.

The results advanced our knowledge a good deal: cervical section has no effect on O_2-consumption, whilst dorsal section is followed by a rise of 50–60%. I wish to add that the animals were kept warm so that no necessity of increased oxidation for thermoregulatory purposes could have arisen. This increased O_2-consumption was taken by earlier investigators for chemical thermoregulation, irrespective of the fact that it is

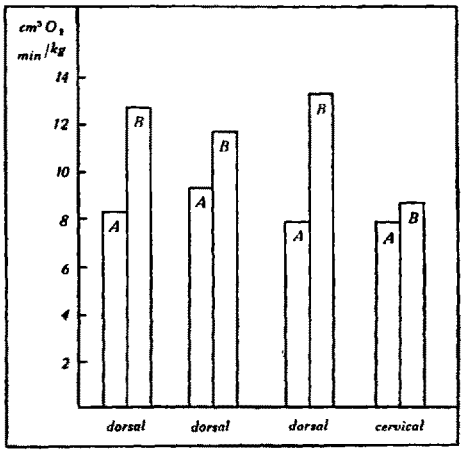

Fig. 9. *A* = before section of spinal cord
B = after section of spinal cord

present in a warm environment as well. The only difference between cervical and dorsal transsection in this respect is that in the latter case there is no necessity to furnish the fuel for excessive combustion from outside; the flame burns high as long as there is some fuel left in the stores of the body. The ability to adjust loss and production of heat is lost equally in both instances.

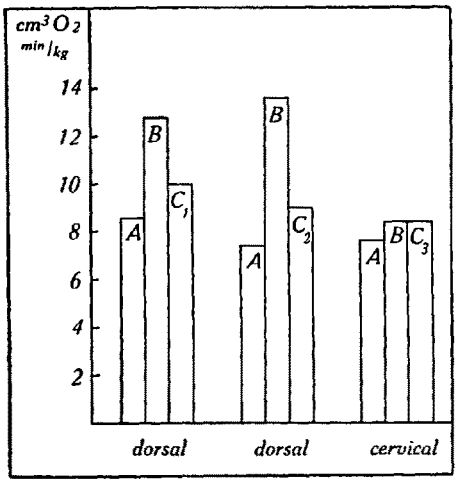

Fig. 10. *A* = normal
B = after section of spinal cord
C = after thyreoidectomy

A constantly high rate of oxidation, as observed in animals with dorsal section of the spinal cord, naturally suggests an increased function of the thyroid as a possible cause. Therefore thyroidectomy was performed on animals with dorsal transsection. The result was that following thyroidectomy O_2-consumption gradual-

[1] H. FREUND and E. GRAFE, Arch. exp. Path. u. Pharm. *70*, 135 (1912).
[2] K. OBERDISSE, Arch. exp. Path. u. Pharm. *162*, 150 (1931).

ly declined and reached in approximately 4 weeks a normal level.

Simultaneously with the decline of the rate of metabolism the so-called thermoregulation deteriorates—a most significant fact, because otherwise thermoregulation tends towards improvement with time (see Fig. 11).

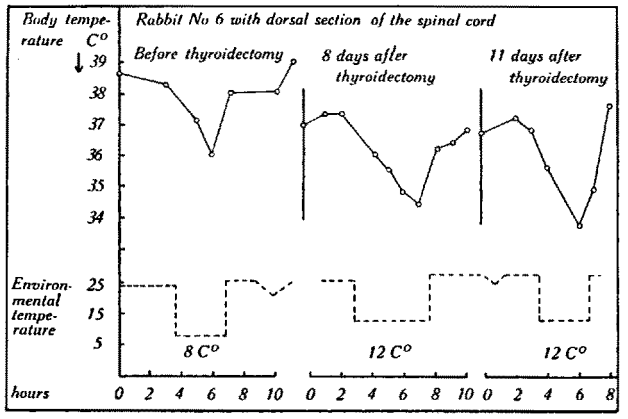

Fig. 11.

Summing up this aspect of the problem one may say that the ability of animals with cervical section to maintain body temperature in a moderate climate is due exclusively to excessive combustion of foodstuffs, while in animals with dorsal transsection a constant rise of the rate of metabolism is observed which is equally independent of external temperature, but is due to hyperfunction of the thyroid gland. There remains of course to consider whether an increased production of thyroxine, or a decreased production of thermothyrin, or both are responsible for excessive O_2-consumption. At this moment it would be premature to make a definite statement on this problem—though it is not improbable that changes in thermothyrin production play a significant role.

There seems no doubt that this difference in thyroid function observed in cervical and dorsal section is due ultimately to interference with the innervation, therefore the next figure may illustrate this *as derived from experimental results* (see Fig. 12).

From all these experiments the conclusion may be drawn that THAUER'S and POPOFF'S experiments, though most interesting in themselves and leading to valuable further information, fail to prove the existence of a thermoregulation independent of the regulatory centre.

Recently our knowledge advanced even somewhat further. ISSEKUTZ, jun.[1], explained the results of THAUER and POPOFF by assuming that, the vagi and some sympathetic fibres remaining intact after cervical transsection of the spinal cord, those may be responsible for the thermoregulatory phenomena observed in these animals. This assumption he was able to substantiate by demonstrating that section of these nervous pathways abolishes even the remnants of thermoregulation. In these experiments the section of the last nerve fibres is associated with such a fall of blood pressure that no cerebral regulative function could be expected. He therefore devised another experiment to eliminate this objection[1]. O_2-consumption of the lower extremity of dogs on which cervical section had been performed was measured with and without cooling of the head. The result was that cooling of the head increased O_2-consumption of the lower limb until the last nervous pathway, the sympathetic (lower cervical and stellar ganglia), was transsected.

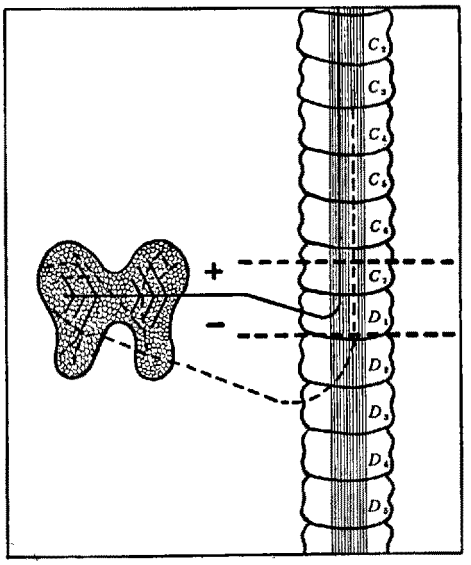

Fig. 12.

These experiments of ISSEKUTZ were of the highest interest to me because, probably without his knowledge, they confirmed some old observations of mine, that striated muscle receives impulses through the sympathetic that increase oxidation. NAKAMURA[2] in BARCROFT'S laboratory was unable to confirm my results—evidently because his experiments were performed in deep anæsthesia, and, as ISSEKUTZ pointed out, even light anæsthesia abolishes this form of thermoregulation..

However great my satisfaction naturally was at the confirmation of experiments performed 30 years ago, it seemed to me wiser to wait for further developments. (1) It had to be considered that the O_2-consumption of an organ can be measured accurately only if both blood gas analysis and estimation of blood flow are accurate. In his last paper read before the Academy ISSEKUTZ, sen., mentioned that the Rein-Stromuhr they used needed readjusting, and so we must wait till these very laborious experiments are repeated and confirmed.

[1] B. ISSEKUTZ, jun., Pflügers Arch. *238*, 787 (1937).

[1] B. ISSEKUTZ, jun., Pflügers Arch. *247*, 204 (1943).
[2] H. NAKAMURA, J. Physiol. *55*, 100 (1921).

(2) The second factor that curbs my satisfaction originates from our own most recent experiments.

In these we measured O_2-consumption of dogs with cervical transsection of the spinal cord:

(a) during cooling of the distal part of the animal,

(b) during cooling of the head.

The results were at first disturbingly inconsistent, later rather unexpected.

Cooling of the head while the distal part of the animal was kept warm had no effect on O_2-consumption. In experiments in which the lower parts were cooled and the head kept warm, O_2-consumption increased and the muscles of the warmed head started to shiver. Yet —alas—these results were quite inconsistent, in other cases just the reverse was observed: O_2-consumption rose if the head was cooled and remained unchanged if the lower half was cooled. The confusion seemed absolute—no rule whatsoever. Just on the verge of exasperation, an idea occured to me; following this further I introduced a long thermometer through the rectum high up into the colon almost to the left colonic flexure. This simple procedure was the key of the confusing riddle.

The readings of the colonic temperature showed without any shadow of doubt that no wonder the results were inconsistent, because shivering is elicited exclusively by subnormal temperature of the blood, that it is absolutely indifferent which part of the body is cooled, and that the sensory nerves of the skin have nothing to do with this mechanism. This regulating mechanism is a very accurate one; no shivering and therefore no rise of O_2-consumption was observed until the dog's temperature had declined below 38·6 C^0, which was their normal temperature. Yet if temperature declined only by 0·1 C^0 below this level, shivering set in the muscles of the proximal (innervated) half, quite independently of whether innervated or not innervated parts were cooled. Thus ultimately the riddle, that cooling of the innervated proximal half may not be followed by shivering, whilst cooling of the not innervated part produced shivering, and why in some cases the reverse was the case, was solved.—At the same time these experiments prove convincingly that the regulative action of blood temperature, discovered by BARBOUR[1] in H. H. MEYER's Institute and thought to be of secondary importance, is responsible for evoking shivering, and not impulses originating from sensory nerve endings in the skin, as believed and taught hitherto.

This discovery is—alas—not quite new. UPRUS, GAYLOR, and CARMICHAEL[2] observed in 1935 a patient with transverse lesion of the spinal cord and demonstrated that shivering of the proximal (innervated) muscles can be produced by cooling of the distal, not innervated parts only if cooling is associated with a fall of rectal temperature. The same was observed by ISSEKUTZ[1]. Definitely new in our observation is the fact that *cooling of the innervated part of the body also produces shivering only if it leads to a fall of blood temperature.*

Two simple everyday observations, which may be tested by everybody thus can be explained:

(1) If somebody walks out from a hot bath, which has raised the blood temperature, into the cold, 10 or even 20 minutes will elapse until he starts to shiver—though one would think that the stimulation of the sensory nerve endings in the skin is by contrast even greater. The lag is due to the fact that it takes some time till blood temperature declines to a level that elicits shivering.

(2) We must not feel any more astonished that ladies with a fair degree of decolletage do not shiver, if only the other parts of the body are covered adequately for maintaining blood temperature above the level eliciting shivering. Not only do they not shiver, they have no sensation of being cold—another proof that the sensation of being cold is not due to stimulation of sensory nerve endings.

Knowing all this, the importance of hormonal thermoregulation can be understood more easily. There would be little sense in the production of chemical agents for increasing heat production and consecutively blood temperature if shivering were due to impulses originating from the sensory nerve endings in the skin and were therefore independent of blood temperature. The importance of hormonal thermoregulation lies in the fact that by increasing heat production it tends to raise blood temperature and so prevents shivering by maintaining blood temperature above the level that elicits shivering. Shivering is the emergency mechanism of thermoregulation and is resorted to if the limits of hormonal thermoregulation are exceeded.

I hope that this necessarily limited survey of thermoregulation was able to show how hormonal and nervous mechanism are combined to a functional unit, and how their interaction represents perhaps the most nearly perfect regulation encountered in the sphere of life.

Zusammenfassung

Es wird über Untersuchungen zur Frage der *hormonalen* und *nervösen* Wärmeregulation berichtet. Die Ergebnisse lassen sich wie folgt zusammenfassen:

1. Werden Tiere abgekühlt, so vermag ihr Blutserum (nach Befreiung von Eiweiß- und Lipoidstoffen) die Verbrennungen im ruhenden Muskel zu steigern. Diese Fähigkeit des Blutserums ist an die Tätigkeit der Schilddrüse *und* der Hypophyse geknüpft. Das durch die Kältewirkung produzierte Thyroxin veranlaßt die Hypophyse, einen Wirkstoff («Heizhormon») zu sezernieren. Dieser treibt die Oxydationen im Muskel unverzüglich in die Höhe. Das Thyroxin steigert erst 24 Stunden später die

[1] H. G. BARBOUR, Arch. exp. Path. u. Pharm. *70*, 1 (1912).

[2] V. UPRUS, J.B. GAYLOR, and E.A. CARMICHAEL, Brain *58*, 220 (1935).

[1] B. ISSEKUTZ, jun., Pflügers Arch. *247*, 204 (1943).

Oxydationen in den inneren Organen, den kalorischen Effekt des Muskelzitterns und den Tonus der Hautgefäße. Hierdurch wird der hormonale Kälteschutz weitergefördert.

2. Werden Tiere erwärmt, so sezerniert die Schilddrüse einen die Verbrennung hemmenden Wirkstoff, das Thermothyrin A, und — in der warmen Jahreszeit — einen zweiten Stoff gleicher Art, das Thermothyrin B. Beide sind in kristallisierter Form darzustellen; ihre Bruttoformeln sind $C_{20}H_{40}O$ bzw. $C_{20}H_{42}$. Schilddrüsenlose Tiere zeigen eine abgeschwächte Wärmetoleranz, was auf das Fehlen dieser «Kühlhormone» zurückzuführen ist.

3. Bei einer näheren Prüfung der nervösen Wärmeregulation ergibt sich — im Gegensatz zu den Ergebnissen von THAUER und POPOFF — daß nach Durchtrennung des Hals- und Brustmarks die chemische Wärmeregulation aufgehoben ist. Diese wird am Halsmarktier dadurch vorgetäuscht, daß alle verzehrte Nahrung verbrannt wird: die Fähigkeit, Nahrungsreserven zu stapeln, geht verloren. Am Brustmarktier werden die Oxydationen durch eine ungehemmte Schilddrüsentätigkeit gesteigert. Damit wird die Wärmebildung, unabhängig von der äußeren Temperatur (also auch in warmer Umgebung) weit über die Norm erhöht.

4. Bei der nervösen Wärmeregulation wird, das ergeben weitere Untersuchungen, die vermehrte Wärmebildung durch Muskelzittern nicht von den Kälterezeptoren der Haut, sondern allein von der verminderten Bluttemperatur ausgelöst. Das zeigt den eigentlichen Nutzen der hormonalen Faktoren des Kälteschutzes.

Über Substitutionsgene und Transfer der Genfunktion

Von CURT KOSSWIG[1], Istanbul

In den letzten Jahren sind eine Reihe von Ergebnissen genetischer Untersuchungen bekanntgeworden, welche eine teilweise Revision unserer Anschauungen phylogenetischer Entwicklungen erforderlich zu machen scheinen. Hierüber soll im folgenden kurz berichtet werden.

Ziel aller Untersuchungen der klassischen Genetik war es, die an der Ausbildung eines Merkmals beteiligten Gene in ihrem Erbgang möglichst genau zu erkennen, ihren Lokus möglichst sicher zu bestimmen. In allen derartigen Genanalysen wurde aus verständlichen Gründen mit leicht im Phänotyp erkennbaren Genen gearbeitet, von denen die meisten auf Grund «großer» Mutationen bei den Haustieren des Genetikers aufgetreten waren. Nur kleine Abweichungen im Phänotyp schaffende Gene sind «unpraktisch». Die Untersuchung «großer» Mutationen hat in zahlreichen Fällen gezeigt, daß ein kompliziertes Zusammenspiel vieler nicht alleler Gene an der Hervorbringung der «typischen» Beschaffenheit eines Merkmals beteiligt ist. Erinnert sei nur an die zahlreichen Gene, die bei *Drosophila* Augenfärbung oder Flügelbildung, bei *Antirrhinum* Chlorophyllentstehung oder Blütenfarbe beeinflussen. Die verschiedenen Gene, die gemeinsam an der Hervorbringung eines Merkmals beteiligt sind, wirken dabei entweder gleichsinnig (Polymerie), oder sie stehen zueinander in einem komplementären Verhältnis, oder eins ist die Voraussetzung für das Aktivwerden eines oder mehrerer anderer (Epistasie). Andererseits beeinflußt ein Gen in der Regel nicht nur ein Merkmal; es ist vielmehr pleiotrop. Von den Genen A, B, C und D, welche in bestimmter hierarchischer Ordnung ein Merkmal M_1 hervorbringen, wirkt z. B. C mit F, G und H zusammen in einem anderen Genkomplex bei der Kontrolle des Merkmals M_2 usw. So entsteht ein höchst kompliziertes System von wechselseitigen Beziehungen von Gengruppen zueinander. Gene einer Gruppe, welche bei der polyfaktoriellen Kontrolle *eines* Merkmals eine Rolle spielen (Polygenie), gehören eben dank ihrer Pleiotropie auch in mehrere andere Gruppen.

Es kann keinem Zweifel unterliegen, daß das Modell, welches uns die Untersuchungen an unseren genetischen Haustieren bieten, auch für die Entstehung der Merkmale der natürlichen Formengruppen gilt. Nur insofern besteht ein gradueller Unterschied, daß die in der Natur gefundenen Verschiedenheiten zwischen verwandten und noch miteinander kreuzbaren Formen, auch wenn nur ein Merkmal in Betracht gezogen wird, nur sehr selten auf einem oder einigen wenigen differenten Allelenpaaren beruhen. Selbst geringfügige Färbungsunterschiede zwischen geographischen Rassen, z. B. bei *Peromyscus* (SUMNER[1]), sind durch mehrere Genpaare mit $\pm$ polymerer Wirkung hervorgerufen; dabei sind diese polyfaktoriellen Unterschiede immer noch kleiner als zahlreiche monofak. toriell bedingten genetische unserer Versuchsobjekte, die in Domestikation entstanden sind.

Einer genetischen Analyse im Sinne der klassischen Genetik bereiten polymer bedingte Merkmale sehr erhebliche Schwierigkeiten, denn die Verfolgung eines Gens durch Generationsfolgen ist praktisch unmöglich, sobald nur einige (etwa 4) Genpaare mit additivpolymerer Wirkung beteiligt sind. In F_2 einer tetrahybriden Kreuzung, in der $ABCD$ gleichsinnig wirkende Gene darstellen, von denen jedes z. B. die Färbung im gleichen Umfang verdunkeln möge, erkennen wir bei sehr großer Individuenzahl zwar noch die Aufspaltung in verschieden intensive Farbklassen in binomialer Verteilung, ob aber in der schwach ge-

[1] Zoologisches Institut der Universität Istanbul.

[1] F. B. SUMNER, Bibliogr. genetica *9*, 1 (1932).