curves are determined. This area is given by the formula $F s^2$, where $F$ is the area of the superimposed curve for a given scale and $s$ the linear magnification with respect to the same scale. This picture evaluation, realizable with simple accessories, makes it possibly to carry out the required area determination rapidly and surely with an error of only $\pm 0{\cdot}3\%$, and the experimental work is considerably reduced.

The method of electrophoresis is, according to its conception and development, an analytical one, the value of which is chiefly evident in investigations on natural substances of high molecular weight, especially proteins and proteids. It is also, however, so far as the stability of interfaces of increasing size can be maintained, of importance for the preparation of small quantities of pure substances of this type. Finally, it is one of the best methods of controlling the working out and carrying through of preparative methods for substances of high molecular weight on a larger scale[1].

The analytical value of electrophoresis is not diminished by the fact that only positive results, such as cannot be obtained, as a rule, except from a series of experiments, can prove the purity and homogeneity of a material examined, and that it seems to be important in every case to confirm these results by taking into consideration other suitable methods of investigation[2]. The ultracentrifuge[3], and diffusion measurements[4], may be considered as the most important of such methods. The methods and results of the ultracentrifuge are widely known through the brilliant work of SVEDBERG, so that it is hardly necessary to go into them; it may not be so well known that the diffusion measurements introduced by LAMM are of high value for controlling the purity of proteins, as only pure substances give a diffusion curve which corresponds exactly to that of the ideal distribution curve of Gauß.

The survey which has been given above on the subject of electrophoresis traces its development by LONGSWORTH, SVENSSON and other research workers from the initial pioneer experiments of TISELIUS. New progress is described in technique and methods which has been achieved in America, Sweden and Switzerland permitting both an increase in accuracy and a facilitation of the experimental procedure. The importance of electrophoresis, especially for protein research is emphasized and the continued expansion in its field of application, as reflected in the great increase in literature on this subject, is illustrated. The extent of this field is indicated and it is also pointed out that it is an advantage to confirm, supplement and amplify the results with the aid of other suitable methods such as the ultracentrifuge and diffusion measurements.

The author wishes to express his thanks to Prof. A. STOLL for his support throughout the course of his work.

*Zusammenfassung*

Es wird ein Überblick über die Elektrophorese gegeben, wie sie aus den grundlegenden Arbeiten von A. TISELIUS hervorgegangen und von L. G. LONGSWORTH, H. SVENSSON und anderen Forschern ausgebaut worden ist. Neuere Fortschritte der Technik und Methodik, die in Amerika, Schweden und der Schweiz erzielt werden konnten und sowohl eine Erleichterung der Versuche wie eine Steigerung der Meßgenauigkeit ermöglichen, werden besprochen. Die Bedeutung der Elektrophorese, insbesondere für die Proteinforschung, wird hervorgehoben und es wird auf die zunehmende Verbreitung der Elektrophorese hingewiesen, die sich in einem erheblichen Anwachsen der einschlägigen Literatur spiegelt. Leistungsfähigkeit und Anwendungsbereich der Elektrophorese werden umrissen mit dem Hinweis darauf, daß es zumeist von Vorteil ist, die Ergebnisse mit Hilfe anderer geeigneter Methoden (Ultrazentrifugierung, Diffusionsmessung usw.) zu sichern, zu ergänzen und zu erweitern.

[1] E. J. COHN, T. L. MCMEEKIN, J. L. ONCLEY, J. M. NEWELL, and W. L. HUGHES, J. Am. Chem. Soc. *62*, 3386 (1940). – E. J. COHN, J. A. LUETSCHER jr., J. L. ONCLEY, S. H. ARMSTRONG jr., and D. B. DAVIS, J. Am. Chem. Soc. *62*, 3396 (1940). – J. W. WILLIAMS, M. L. PETERMANN, G. C. COLOVOS, M. B. GOODLOE, J. L. ONCLEY, and S. H. ARMSTRONG jr., J. Clin. Invest. *23*, 433 (1944). – S. H. ARMSTRONG, jr., M. E. J. BUDKA, and K. C. MORRISON, J. Am. Chem. Soc. *69*, 416 (1947).

[2] E.g. A. STOLL and E. WIEDEMANN, Schweiz. med. Wschr. *77*, 664 (1947).

[3] TH. SVEDBERG and K. O. PEDERSEN, The Ultracentrifuge. Clarendon Press, Oxford 1940. – E. G. PICKELS, Chem. Rev. *30*, 341 (1942).

[4] O. LAMM, Nova Acta reg. Soc. Sci. Upsaliensis *10*, 6 (1937). – H. NEURATH, Chem. Rev. *30*, 357 (1942).

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

By G. MANSFELD[2], Budapest

The fact that VAN 'T HOFF'S rule is valid for living matter throws adequate light on the importance of the regulation of temperature, perhaps the most perfect regulatory mechanism evolved in the course of phylogenesis. Differences of a few tenths of a degree Centigrade may indicate disease, and neither the heat of the tropics nor the cold of the Arctic changes our body temperature. Inquiry about the mechanism of this most precise regulation is usually answered by comparing it to the thermostat. A more adequate metaphor is supplied by a gas-heated room in which the height of the flames and the rate of ventilation are strictly coordinated; an increase of the height of the flames is associated with a precisely adequate rise of the rate of

[1] A lecture.

[2] Institute of Physiology, University of Budapest.

ventilation, and increased ventilation is followed automatically by a strictly proportional increase of combustion.

The two factors of thermoregulation in the animal organism are: (1) heat production, or, in other words, the rate of metabolism, depending on oxïdative processes in the cells, (2) the loss of heat through vasodilatation in the skin, perspiration, and respiratory ventilation. The two factors, heat production and loss of heat, are in a remarkable equilibrium; therefore the question as to the nature and location of the regulatory mechanism arises. It is well known—and nobody doubted it until recently—that this coordination is accomplished by the central nervous system through centres located in the diencephalon. This contention is based on two facts: (1) CLAUDE BERNARD[1] demonstrated that section of the cervical spinal cord is followed by poikylothermia, (2) ARONSON and SACHS[2] found that stimulation of a certain circumscript diencephalic region is followed by increased production and decreased loss of heat, a response leading consequently to a rise of body temperature, with other words to fever[3].

Regulation of temperature seemed at this stage of affairs a relatively simple process and was accordingly taught all over the world as follows: Cold stimulates the sensory nerve endings in the skin, from there impulses are transmitted to the thermoregulatory centre and there elicit two effects: (a) vasoconstriction in the skin via vasoconstrictor nerve fibres (diminution of ventilation), and (b) stimulation of nerve fibres that stimulate oxidation in organs and especially in muscle, this being associated in the latter with shivering. Heat diminishes the activity of the thermoregulatory centre; vasodilatation in the skin, cessation of shivering, and reduced oxidation are the effect.

During the last decades a number of facts were established that could not be fitted into this rather simple scheme, and about these experimental facts and the conclusions that necessarily follow, I am permitted to-day to address you.

One factor which raised doubt in regard to the simple and appealing mechanism mentioned before, weighs—excepting A. MONTUORI'S[4] forgotten observation—on my conscience. As a consequence of this sin of my youth, I am condemned since 40 years to forced labor on this problem and as some compensation have been able to demonstrate the existence of specific hormones concerned with the regulation of body temperature. In the other work that casts doubt on the accepted theory I was only an accomplice, the chief malefactors being THAUER[5] and POPOFF[6], who independently of each other astonished the scientific world one day by the statement that loss of thermoregulation following section of the cervical spinal cord is only transitory; after 5–6 days the animal regains the ability to regulate its body temperature—though to a lesser degree. This observation established the existence of a mechanism regulating body temperature independently of the centre.

In order to be able to discuss the main problems of thermoregulation as they present themselves to-day within an hour, I am compelled to restrict myself to one factor and so forced to exclude the other—loss of heat, in other words everything that is included in the term physical thermoregulation—completely. This I can do the more easily because—with a single exception of minor importance, to which I shall refer later—our concepts of this problem have not been altered essentially during the last years. All our attention must be focussed on the first factor, the changes and control of heat production, with other words on those regulatory mechanisms which since RUBNER[1] are designated by the term of *chemical thermoregulation*. At this point I must recall an old and bitter contest, waged between RUBNER[2] and ZUNTZ[3] at the turn of the century; a contest in which no definite decision was reached, but which grew more and more embittered and ultimately swelled to dimensions of the deadly clash of two diametrically opposed creeds—called Weltanschauung by the Germans.

RUBNER believed that cold through an undefined mechanism brings about increased oxidation in the muscle even in the absence of shivering, without increasing tonus, and besides this also increases oxidation in various organs, for instance in the secretory glands and especially in the liver. This increased heat production—in the absence of increased specific activity, in other words organs at complete rest—was termed by RUBNER chemical thermoregulation. ZUNTZ, who did not appreciate intuition in the absence of clear-cut convincing evidence, fiercely opposed this view and adhered to the doctrine that visible muscular activity is the only mechanism acting through increased oxidation in thermoregulation.

Ultimately experiments not even devised for elucidating this problem decided this contest. Considering the effect of puncturing the thermoregulatory centre (Wärmestich), it seemed rather startling that a single stimulus is followed by increased heat production lasting for several days. The explanation offered by the then universally adopted theory—that this increase was due to nervous impulses reaching the peripheral organs continuously for a prolonged period—seemed, in view of everything we knew about the activity of the nervous system, rather improbable. Therefore I

[1] CL. BERNARD, Leçons de pathologie expérimentale. Paris 1871.
[2] E. ARONSON and G. SACHS, Dtsch. med. Wschr. (1884).
[3] CH. RICHET, Pflügers Arch. *37*, 624 (1885).
[4] A. MONTUORI, Ricerche biotermiche. Napoli 1904.
[5] R. THAUER, Pflügers Arch. *236*, 102 (1935).
[6] N. F. POPOFF, Pflügers Arch. *234*, 137 (1934).

[1] M. RUBNER, Die Gesetze des Energieverbrauchs bei der Ernährung. Leipzig 1901.
[2] M. RUBNER, Arch. Hygiene *11*, 287 (1890).
[3] N. ZUNTZ and G. RÖHRIG, Pflügers Arch. *4*, 57 (1871).

assumed as a working hypothesis that stimulation of the thermoregulatory centre acts through eliciting the production of substances, perhaps hormones, that increase oxidation in the cells; and that, once set going, this mechanism runs its course without needing further stimulation from the centre. Eight years before WARBURG published his method, it was not possible to measure the $O_2$-consumption of cells, therefore the measuring of the consumption of a substrate seemed the only available approach for solving the problem[1]. So we measured the sugar consumption of isolated hearts of normal and fevering rabbits[2]. These experiments showed that 70% more glucose was consumed by the hearts of animals in which puncture of the thermoregulatory centre had been performed. The evidence seemed conclusive: stimulation from the centre is not responsible for sustaining the effect, therefore something else must do it. At this stage our work suffered an interruption of 4 years through world war I. In 1919 we were at last able to start to investigate physiological thermoregulation[3]. In the course of this investigation we were able to demonstrate that (1) hearts of rabbits kept in the cold consumed considerably more glucose than hearts of animals kept in a warm environment, (2) that sera of animals exposed to cold increase, and sera of animals kept warm decrease sugar consumption of isolated hearts.

*Table I*

Sugar consumption of isolated rabbit hearts pro g and hour

| Without serum | With serum |
|---|---|
| Cooled animals | |
| 1·51 | 0·69 |
| 2·28 | 0·94 |
| 3·60 | 0·41 |
| 2·80 | 1·22 |
| 2·92 | 0·97 |
| Mean: 2·62 | 0·84 |
| Heated animals and summer animals | |
| 0·85 | — |
| 1·00 | — |
| 0·80 | 2·57 |
| 0·27 | 2·82 |
| 0·58 | 3·56 |
| 0·80 | 3·46 |
| Mean: 0·71 | 3·10 |

This observation seemed to be of fundamental importance: both exposure to cold and heat are associated with the production of substances affecting cellular oxidation. The next important step was the demonstration that sera of thyroidectomized animals, obtained under similar circumstances, had no effect whatsoever. We naturally concluded that both principles, the one increasing oxidation—which was plausible—and the other decreasing oxidation—which was rather remarkable, are produced by the thyroid.

These experiments elucidated the problems of thermoregulation considerably and brought out a—so far unknown—hormonal mechanism centering in the thyroid.

Further data, laboriously collected in order to throw more light on these problems, progressively darkened our field of vision—just as light diminishes as tunnelling proceeds deeper and deeper. The discovery of thyroxine, the active principle of the thyroid, blurred our vision completely. A latency of 24 hours in the intact animal! The whole problem had to be investigated over again.

*Table II*

The effect of 5 $cm^3$ serum of cooled normal animals on $O_2$-consumption of muscle

| Date 1938 | Blood spender | Blood reicever | $O_2$-consumption ($mm^3$ per g and hour) before serum injection | $O_2$-consumption ($mm^3$ per g and hour) after serum injection | Difference % |
|---|---|---|---|---|---|
| 11. XI. | A | 1 | 207 | 337 | + 62 |
| 14. XI. | B | 2 | 180 | 246 | + 36 |
| 25. XI. | C | 3 | 186 | 286 | + 54 |
| | | 4 | 213 | 224 | + 5 |
| 30. XI. | D | 5 | 203 | 266 | + 31 |

So we started to investigate the effect of sera obtained from cooled animals on the oxidation of muscle, using WARBURG's method[1].

The results were clear-cut: sera of cooled animals increased the $O_2$-consumption of muscle considerably and —without latency; sera of thyroidectomized animals had again no effect (see Table III). Therefore the

*Table III*

Effect of 5 $cm^3$ serum of cooled *thyroidectomized* animals on $O_2$-consumption of muscle

| No. of experiment | Date | Blood spender (thyroidectomized) | Blood receiver | $mm^3$ $O_2$/consumption per g muscle and hour before serum injection | $mm^3$ $O_2$/consumption per g muscle and hour 30′ after serum injection | Difference % |
|---|---|---|---|---|---|---|
| 5 | 28. XI. | E | 6 | 237 | 239 | 0 |
| | | | 7 | 263 | 262 | 0 |
| | | | 8 | 264 | 234 | −11 |
| | | | 9 | 221 | 234 | + 5 |
| 6 | 29. XI. | F | 10 | 242 | 207 | −10 |
| | | | 11 | 251 | 293 | +16 |
| | | | 12 | 231 | 253 | +13 |
| 7 | 9. XII. | G | 13 | 309 | 292 | − 5 |
| | | | | 234 | 239 | + 2 |

[1] F. S. LOCKE and O. ROSENHEIM, J. Physiol. *36*, 205 (1907).

[2] G. MANSFELD, Zbl. Physiol. *27*, 267 (1913); Pflügers Arch. *161*, 430 (1915).

[3] G. MANSFELD and L. v. PAP, Pflügers Arch. *184*, 281 (1920).

[1] G. MANSFELD, Arch. exp. Path. u. Pharm. *196*, 573 (1940).

question had to be asked whether thyroxine has anything at all to do with the observed effect of the sera of cooled animals.

A series of experiments, the results of which were rather difficult to interprete at first in themselves, viewed together elucidated our problem. *Sera* of animals that had received thyroxine 1–3 hours earlier ("Thyroxinsera") augmented the $O_2$-consumption of muscle in the same manner as sera of cooled animals

*Table IV*

Effect of "Thyroxinsera" on $O_2$-consumption of muscle

| Date 1939 | Blood spender (after 0·5 mg Thyroxine) | Blood receiver (normal) No. | $O_2$-consumption ($mm^3$ per g and hour) before serum injection | $O_2$-consumption ($mm^3$ per g and hour) after serum injection | Difference % |
|---|---|---|---|---|---|
| 17. III. | H | 15 | 216 | 293 | + 35 |
| | | 16 | 186 | 273 | + 46 |
| | | 17 | 128 | 267 | +108 |
| 18. III. | I | 18 | 233 | 280 | + 20 |
| | | 19 | 159 | 293 | + 84 |
| | | 20 | 176 | 262 | + 48 |

(see Table IV). We knew that thyroxine itself has no direct effect on the oxidation of muscle in Warburg's apparatus under similar conditions[1] and therefore had to conclude that thyroxine elicited the production of another substance—probably the same that is effective in the serum of cooled animals. It seemed rather probable that another endocrine gland may be concerned with the production of this principle. Reviewing all the data concerned, it seemed to us that the adrenals and the pituitary must be first considered. Experiments showed that sera of hypophysectomized animals had no effect on oxidation of muscle following injection of thyroxine, nor could an effect be observed from sera of hypophysectomized animals after exposure to cold[2] (see Table V).

*Table V*

Effect of 5 $cm^3$ serum of cooled *hypophysectomized* animals on $O_2$-consumption of muscle

| Date 1939 | Blood spender (hypophysectomized) | Blood receiver (normal) No. | $O_2$-consumption ($mm^3$ per g and hour) before serum injection | $O_2$-consumption ($mm^3$ per g and hour) after serum injection | Difference % |
|---|---|---|---|---|---|
| 28. III. | P | 31 | 237 | 245 | +3 |
| | | 32 | 211 | 214 | ±0 |
| 29. III. | Q | 33 | 294 | 286 | −3 |
| | | 34 | 250 | 261 | +4 |

[1] G. MANSFELD, Arch. exp. Path. u. Pharm. *193*, 231 (1939).

[2] G. MANSFELD, "Die Hormone der Schilddrüse und ihre Wirkungen". Benno Schwabe & Co., Basel 1943.

These results were interpreted to signify that the thermoregulatory reaction to cold involves the *interplay of two endocrine glands*: the thyroid reacts to cold by an immediate increase of thyroxine output, the consecutively increased thyroxine level of the blood stimulates in the pituitary the secretion of the active principle, termed by us the *"heating hormone"*. This heating hormone is responsible for the observed immediate increase of oxidation and may therefore be considered as the most important positive factor in chemical thermoregulation. The activity of sera containing the heating hormone is not affected by removal of proteins and lipids[1].

Production of the heating hormone of the pituitary is the most important, but by no means the only hormonal response to cold. Thyroxine, which elicits the secretion of the pituitary heating hormone, increases oxidation also—but after a latency of approximately 24 hours. We were able to demonstrate that 24 hours after the animals were exposed to cold, the $O_2$-consumption of liver tissue is considerably increased (see Table VI), evidently corresponding to the delayed

*Table VI*

$O_2$-consumption of liver tissue before and 24 hours after exposing animals to cold

| Date 1940 | $O_2$-consumption of one g liver tissue per hour before exposing to cold | $O_2$-consumption of one g liver tissue per hour 24 hours after exposing to cold | Difference % |
|---|---|---|---|
| 9. II. | 546.8 | 741·9 | +36 |
| 9. II. | 473·2 | 661·9 | +40 |
| 10. II. | 448·3 | 651·9 | +45 |
| 10. II. | 566·0 | 745·2 | +32 |

action of thyroxine *per se*[2]. The physiological importance of this mechanism in prolonged exposure to cold environment is evident. Besides this action of primary importance, two other effects of thyroxine having a bearing on thermoregulation ought to be mentioned: (1) the increase of vasomotor tonus inhibiting the effect of vasodilators is of some importance in physical regulation, as demonstrated by the inhibition of the fall of body temperature following the injection of novocain[2] (see Fig. 1), (2) the increase of the caloric effect of shivering (see Table VII).

Let us now turn to the effect of heat.

Using essentially the same method, one gastrocnemius of a rabbit was removed before and the other 30 minutes after intravenous injection of 5–10 $cm^3$ serum from another rabbit that previously had been

[1] G. MANSFELD and ESZTER MÉSZÁROS, Arch. exp. Path. u. Pharm. *196*, 590 (1940).

[2] G. MANSFELD and ESZTER MÉSZÁROS, Arch. exp. Path. u. Pharm. *196*, 567 (1940).

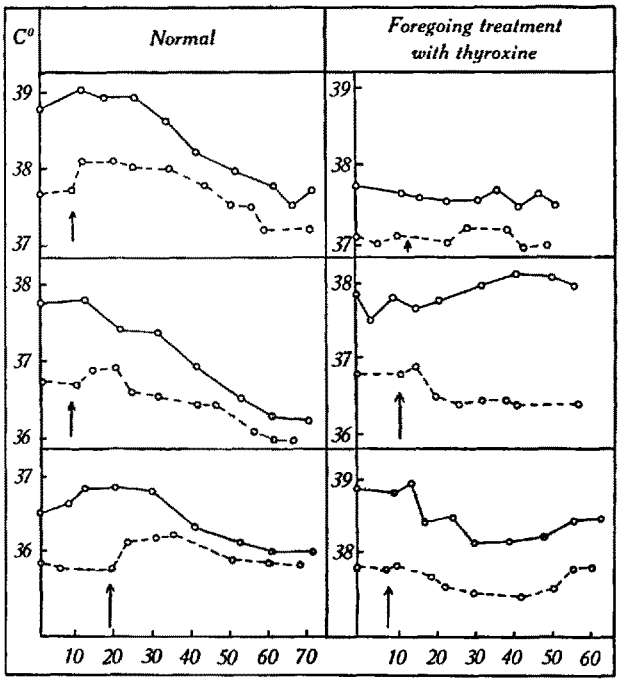


Fig. 1. ↑ = 0·01 g novocain per 100 g guinea pig
—— = rectal temperature
- - - = skin temperature

*Table VII*

Experiments of X. CHACHOWITSCH[1]

| Basal metabolism per kg and hour cal | | The maximum of the metabolism per kg and hour (severe cooling) cal |
|---|---|---|
| Normal | 5·83 | 17·64 |
| Thyroidectomized | 4·90 | 9·31 |
| Normal | 5·14 | 27·97 |
| Thyroidectomized | 3·17 | 14·11 |
| Normal | 7·98 | 36·26 |
| Thyroidectomized | 3·96 | 14·21 |

exposed for some hours to heat, so that a hyperthermia of 1–2° C was produced[2]. Comparison of the $O_2$-consumption of the gastrocnemii showed convincingly that the sera of heated animals contain a principle that reduces oxidation (see Table VIII). Similar results could be obtained from sera after removal of proteins and lipids. And once more—sera of thyroidectomized animals obtained under the same conditions had no effect whatsoever.

Fig. 2 shows the effect of sera of heated animals on the $O_2$-consumption and $CO_2$-production of curarized dogs. The results are essentially similar to those obtained on rabbit muscle: sera of heated normal animals reduce oxidation by 20–30%, while sera of heated thyroidectomized animals are ineffective. Sera of heated hypophysectomized animals are of normal activity. Therefore we may conclude that the pituitary is not involved in the production of the principle that decreases oxidation, while for the production of the heating hormone, as you remember, the pituitary proved to be indispensable.

[1] X. CHACHOVITSCH, C. R. Soc. Biol. *100*, 1220 (1929).
[2] G. MANSFELD, Arch. exp. Path. u. Pharm. *196*, 573 (1940).

*Table VIII*

The effect of serum of heated animals on $O_2$-consumption of muscle

| Number of experiment | $O_2$-consumption $mm^3$ per g and hour before serum injection | $O_2$-consumption $mm^3$ per g and hour after serum injection | Difference % |
|---|---|---|---|
| 8 | 266 | 218 | −18 |
| 9 | 238 | 194 | −18 |
| 10 | 236 | 192 | −18 |
| 11 | 243 | 212 | −12 |
| 12 | 205 | 202 | 0 |
| | 255 | 198 | −22 |
| | 243 | 189 | −22 |
| 13 | 271 | 215 | −20 |
| | 232 | 225 | − 3 |
| | 188 | 201 | + 7 |
| 14 | 227 | 208 | − 8 |
| | 278 | 204 | −26 |

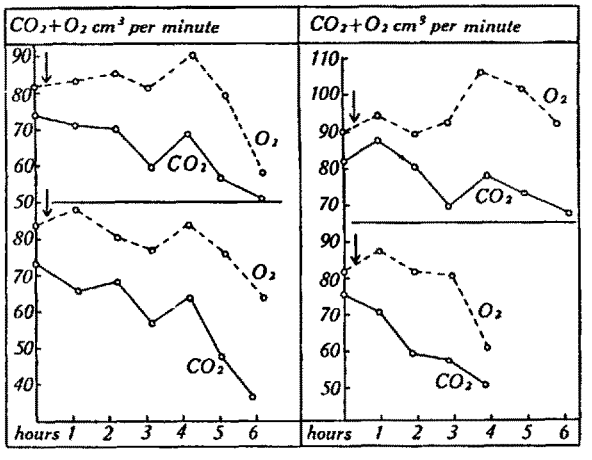


Fig. 2.

Chance brought it about that in the course of an investigation concerned with the mechanism of action of thyroxine we came across some facts pointing in the same direction as the experiments mentioned before. We found that the effect of thyroxine is less during the summer months, but that the animals regain their full sensitivity to thyroxine following thyroidectomy[1]. This seemed to indicate that the thyroid contains—at least in summer—a principle that opposes the action of thyroxine and depresses $O_2$-consumption. Working on this assumption, we were able to prepare from the thyroid gland protein-free extracts containing this

[1] G. MANSFELD and I. SCHEFF-PFEIFER, Arch. exp. Path. u. Pharm. *190*, 565 (1938).

principle, which was termed by us *thermothyrin*. Further analysis demonstrated ultimately that two substances of similar activity but different solubility are present, known to-day as *thermothyrin A and B* respectively.

*Table IX*

Thermothyrin content of sera in different seasons and their effect on metabolism

| Date | Environmental temperature | Maximal change in % of the $O_2$-consumption | Maximal change in % of the $CO_2$-production | Thermothyrin content of 100 cm³ serum in mg: thermothyrin A | Thermothyrin content of 100 cm³ serum in mg: thermothyrin B |
|---|---|---|---|---|---|
| | | in winter | | | |
| 2. XII. 1940 | cold | + 6 | + 9 | 0 | 0 |
| 2. II. 1941 | cold | −10 | − 3 | 0 | 0 |
| 28. XI. 1940 | warm | −40 | — | 10 | 0 |
| 11. XII. 1940 | warm | −26 | −20 | 20 | 0 |
| 12. I. 1941 | warm | −50 | −12 | 11 | 0 |
| | | in spring | | | |
| 7. III. 1941 | cold | −24 | −36 | 0 | 4 |
| 3. V. 1941 | cold | −57 | −67 | 0 | 7,5 |
| 14. V. 1941 | cold (man) | −41 | −26 | 1,5 | 6 |
| 12. V. 1941 | warm | −30 | — | 9,3 | 0,7 |
| 20. III. 1941 | warm | −30 | −34 | 22,0 | 9,0 |
| 16. V. 1941 | warm (man) | −25 | −20 | 4,6 | 1,5 |

The next important advance—isolation in crystalline form—was made after 4 years work by my daughter[1]. Abstaining from details I mention only that data furnished by elementary analysis and freezing point determinations show that the summary formula for thermothyrin A is $C_{20}H_{40}O$, for thermothyrin B $C_{20}H_{42}$, with molecular weights of 296 and 288 respectively. It seems worth while mentioning that the number of C atoms is the same as in vitamin A, and that the latter, according to some investigators has a bearing on thyroid activity. I may add that the pure crystalls are of considerable potency. One mg may reduce the $O_2$-consumption of white rats by 40–46%.

The next problem we had to deal with concerned the physiological function of thermothyrin A and B. Having been able at this time to isolate both thermothyrins not only from the thyroid but from blood serum as well, we proceeded to ascertain laboriously under what conditions each of them appears in the serum[1] (see Table IX).

The results demonstrated clearly that thermothyrin A is present in the blood whenever the animal is exposed to high temperature and shows no seasonal fluctuations, while thermothyrin B is present in the blood only from March to October—but then independently of external temperature. During winter—temperature below +20° C—neither thermothyrin A nor thermothyrin B is present in the blood, and exposure to heat is followed exclusively by production of thermothyrin A. From March to October thermothyrin B is permanently secreted, and the presence of thermothyrin A depends also during this period exclusively on the external temperature. It therefore must be concluded that the two thermothyrins have a distinctly different physiological function. *(To be continued)*

[1] ANNA MANSFELD, Schweiz. med. Wschr. *76*, 439 (1946).

[1] ANNA MANSFELD, Schweiz. med. Wschr. *76*, 439 (1946).

# Différenciation de l'action antimitotique sur la cellule animale normale, *in vitro*

Par R. MEIER et B. SCHÄR[1], Bâle

Les travaux fondamentaux de DUSTIN et de ses élèves (1929–37), concernant l'action inhibitrice de l'alcaloïde du Colchique d'automne sur la division cellulaire, constituent le point de départ d'un grand nombre de travaux en vue de la recherche de substances à action identique. C'est le mérite de DUSTIN[2] d'avoir reconnu que les substances à action antimitotiques attaquent avant tout les tissus qui se trouvent dans un état de croissance accrue. Le premier il étudia l'action de la colchicine sur les tissus de nature maligne. Un grand nombre de savants (v. BRODERSEN[3]) par la suite s'occupa de cette question. Ils constatèrent presque toujours que la colchicine prolonge la survie dans le cas de tumeurs malignes chez l'animal et chez l'homme, mais sans aboutir à une guérison véritable. CRAMER et BRODERSEN[1] parvinrent à des résultats différents en faisant agir la colchicine (resp. la N-éthylcolchicamide), très toxique, à l'usage interne, sous forme de pommade sur des cancers épithéliaux et des cancers du sein. Ils obtinrent un succès curatif complet. C'est ainsi que l'influence des agents chimiques sur le développement de la mitose acquit une grande signification pour la thérapie des tumeurs malignes.

De nombreux savants se sont efforcés par la suite d'élucider plus complètement l'action de la colchicine sur la

[1] Laboratoires scientifiques de la Ciba S.A., Bâle.

[2] P. DUSTIN, Bull. Acad. Méd. Belg. *5*, 14 (1934).

[3] H. BRODERSEN, Strahlentherapie *73*, 198 (1943).

[1] H. CRAMER und H. BRODERSEN, Dtsch. med. Wschr. *70*, 494 (1944).