Eur J Cancer Clin Oncol, Vol. 24, No. 8, pp. 1249–1255, 1988.
Printed in Great Britain

0277-5379/88$3.00+0.00

Perspectives and Commentaries

Thymus and Immunity—I. Early Thymus Research

CHARLES GREGOIRE*
Service de Biochimie, c/o Institut Léon Fredericq, Place Delcour 17, 4000 *Liège, Belgium*

Abstract—*This paper is a review of early results in thymus research that found their full significance after several decades, when the strategic role of the organ in immunology was recognized.*

EPITHELIAL CELLS, LYMPHOBLASTS, LYMPHOCYTES AND THYMOCYTES

MAXIMOW [1–3] was the first to report that in the embryonic rudiment of the thymus, the interaction between endodermal epithelial cells and immigrated lymphocytes appears as a kind of symbiosis and that the lymphocytes find within the epithelial reticulum conditions for an extremely active proliferation. Maximow described colonization of the epithelial thymic rudiment by lymphocytoid wandering cells becoming lymphoblasts (large basophil lymphocytes) after their penetration in the rudiment. His observations were supported by splendid and convincing drawings. Maximow's concept has been developed by Jolly [4] in numerous contributions on the lymphoepithelial organs.

In the thirties, the controversy between partisans of direct transformation of the thymic epithelium into small lymphocytes [5, 6] and partisans of immigration [1–4, 7] was still active. During that period, important experimental results were obtained. The cortical thymocytes, in contrast to the lymphocytes from the lymph nodes and from the medullary zone of the thymus, were recognized as extremely sensitive to various factors, including X-rays. The reactions of the adult thymus to X-rays (pycnosis, phagocytosis, regeneration) were examined in several studies [8–11]. In the early rudiment [12], the cells of the epithelial reticulum were found relatively radioresistant ([48]; p. 459; [53], p. 67).

The lymphoblasts and the medium-sized lymphocytes resulting from their multiplication were little affected by the X-rays. The highest rate of radiosensitivity coincided with the occurrence of the terminal phases of lymphocyte maturation and with the appearance of the smallest form of lymphocytes, the thymocytes. In the irradiated, more developed fetal organ, the epithelial phagocytes were especially numerous in the perimedullary and in the marginal subcapsular regions, where they appeared as bulging spheroids. Effraction of the capsule by these phagocytes and their liberation into the surrounding connective tissue were especially demonstrative [12]. Regeneration of the cortical region took place mainly by multiplication of the surviving autochthonous medium-sized lymphocytes and probably by centrifugal migration of medullary lymphocytes [13].

Attraction of exogenous lymphocytes by the epithelial cells and their subsequent proliferation in the thymic epithelial reticulum transformed by shrinkage in a solid stroma, were recorded, as a duplication of the histogenetical process, in the course of regeneration of thymus transplants by invading lymphocytes (autologous adult organs [15, 16]; syngeneic grafts of normal primordia [13, 14]). The fragments were implanted in the subcutaneous tissue, in the muscles, in the brain, in the testicles and under the kidney capsule. In the grafts of epithelial thymic rudiments, the primordia of neighbouring organs (trachea, salivary glands) grew anarchically in a relatively empty connective tissue. In contrast, exogenous host lymphocytes were swarming around the thymic implant, illus-

---

Accepted 11 March 1988.

*Address for correspondence and reprints: Dieweg, 292, 1180 Brussels, Belgium.

trating again a specific attraction of the lymphocytes by the thymic epithelial cells.

Within the outlines of the still existing controversy between transformists and partisans of immigration, the results reported above were considered ambiguous by the transformists, because of the participation in regeneration of these grafts of autochthonous surviving cortical thymocytes, and of medullary thymocytes having escaped necrosis of the central part of the graft. Special techniques were then selected [13] in order (a) to implant purely epithelial fragments, (b) to implant these fragments in regions of the host less accessible or inaccessible to invading lymphocytes or (c) in heterologous transplantation, in which the invading lymphocytes could not play any histogenetic role in the donor organ, (d) finally to shelter the fragments in containers impermeable to these cells but permeable to the blood metabolites of the host.

(a) Irradiation of the adult or embryonic thymus before autologous or syngeneic implantation furnished grafts reduced to a circular rim of cortical region composed exclusively of epithelial cells. These conditions were ideal for following the successive stages of regeneration [14]: condensation of the epithelial reticulum into a compact stroma in the form of nodules or rings, considerable gatherings of host small dark lymphocytes around the transplant, in the surrounding blood vessels and lymphatics and active infiltration of the epithelial nodules. The pictures suggested immediately that the thymic epithelial reticulum exerted a considerable attraction on the host lymphocytes, as during the first stages of histogenesis.

At this stage, a reaction, still unreported in the literature, took place in the areas of the implant corresponding to the former subcortical region: once among the epithelial cells on their way to reconstituting a reticulum, the invading small dark host lymphocytes underwent structural alterations. Their nucleus and cytoplasm increased in size, the cytoplasm became strongly pyroninophil. The cells took the cytological appearance of large basophil lymphocytes or lymphoblasts [14]. They restored the capacity for mitotic multiplication. During this relatively short lymphoblastic phase, in which the lymphoblasts were diffusely scattered in the cortical zone, this zone resembled a large, diffuse germinal centre of a lymph node during an active lymphocytopoietic phase. The blastic phase was also recognized during regeneration following irradiation of the thymus *in situ* [13, 14]. This phase might be considered as a repetition of the embryonic process described by Maximow and his student Hartmann [17] in the epithelial anlage. In the implants, the blasts proliferated by mitotic division and were progressively transformed into medium-sized and relatively pale smaller lymphocytes. These lymphocytes of neoformation could be easily distinguished from the newly invading dark small cells. It may also be reported that during the blast phase of regeneration, in grafts of irradiated adult thymus [14], eosinophil granules were found in some of these lymphoblasts, with figures of transition between promyelocytes, myelocytes and metamyelocytes, scattered or grouped in clusters.

Implantation of autologous and syngeneic fragments of irradiated thymus into the large cervical lymph nodes was especially interesting [13], because of the reaction of the host organ. The regeneration of the transplant took place more rapidly than in other regions. The host lymph node was considerably hypertrophied. The germinal centres had multiplied and were strikingly enlarged. After complete regeneration, when recolonization of the implant was completed, the outlines of the thymus grafts were obliterated. When the chimeric lymph node was irradiated at that stage (under shielding of the other parts of the body), within the next 24 h, these outlines reappeared sharply delineated and filled with pycnotic figures, in contrast with the surrounding lymph node tissue containing scattered pycnoses. Conversely, autologous fragments of cervical lymph node transplanted into the neighbouring thymus glands appeared, after regeneration and irradiation, as small areas devoid of pycnotic debris, in the midst of thymic lobules densely filled with pycnotic figures, also the inverse picture of the above reported experiment.

Summarizing the results of irradiations and transplantations, it was assumed [13] that lymphocytes, moderately sensitive to X-rays inside a mesenchymal reticulum, show altered potentialities (mitotic activity, extreme radiosensitivity) after their changes in contact with the cells of the epithelial thymic cortical reticulum.

The hyperplastic response of the host chimeric lymph node to inoculation of thymic epithelial cells suggested the existence in these cells of powerful lymphostimulating substances. In order to investigate the problem, saline extracts were prepared from pig and rabbit thymus reduced to its epithelial components by X-irradiation and cleared from the necrotic thymocyte debris. The extracts were injected subcutaneously to rats [18]. In other groups of rats, fragments of the same material were also implanted. The lymph nodes draining the regions of injection or implantation, compared to the corresponding control lymph nodes on the other side draining extracts of pig and rabbit lymph nodes and muscles, showed slight, though statistically significant, hyperplastic changes, including a lymphoblastic reaction.

(b) Fragments of epithelial rudiments of foetal rabbit thymus implanted in the anterior chamber of the eye, known to be inaccessible or little accessible to the host lymphocytes, survived as purely epithelial formations, in which mitoses were visible [13]. Identical results were obtained with implants of purely epithelial cultures *in vitro* (guinea pig).

(c) Rabbit thymus fragments (rudiments and slightly later stages) were fixed to the chorioallantoic membrane of developing chick embryos. The reaction of the host consisted of a considerable development of capillaries around the implant. The epithelial reticulum of this implant appeared condensed into nodules and crescent-shaped cords, in which mitotic activity continued and around which chick lymphocytoid haemocytoblasts were numerous. No thymocyte developed from these epithelial cells.

(d) In order to shelter the implants from lymphocyte penetration, fragments of normal and irradiated adult and syngeneic embryonic thymuses were introduced in Chamberland–Pasteur filters, wrapped in dead biological membranes (peritoneum impregnated with metallic silver and fixed in alcohol), in folded filter paper, and in porous cellulose membranes (home-made diffusion chambers: the Millipore industry had not yet developed). The bags were placed in the subcutaneous tissue and intraperitoneally. Under these conditions, all the implants remained epithelial. The best results were obtained with transplants wrapped in hydrophil cotton sheets and kept intraperitoneally for several weeks. The reaction of the host against cotton fibres consisted of development of voluminous granulomes made up of several layers of giant cells, which were a highly efficient obstacle against lymphocyte invasion for several weeks, depending on the density and thickness of the sheets. Inside the cotton bags, the epithelial cells formed syncytia of polygonal elements with a pale, abundant cytoplasm, frequently in mitosis and connected together by many intercellular bridges. Perforation of the granulome induced rapid infiltration of lymphocytes. The transplants remained epithelial as long as the lymphocytes could not reach them. In a later work [19], identical results were obtained using Millipore cellulose membranes and thymectomized adult hosts (guinea pigs). The epithelium grew out in the form of nodules, cords and compact sheets.

From the various experimental procedures summarized above, the following general conclusions were drawn [13, 14]:

1. The thymic epithelial components are unable to give rise to thymocytes;
2. The thymic epithelium exerts a considerable attraction and stimulation on the host lymphocytes;
3. The subcapsular blasts must be considered as stem lymphoid cells, proceeding from immigrated lymphoid cells transformed in contact with the cortical epithelial reticulum [13, 14].

A few decades later, in the sixties, during the explosion of literature following the discovery by Burnet and Miller of the immunological function of the thymus, the various kinds of experiments described above, namely the cytological features of recolonization of transplants of irradiated syngeneic thymus have been reproduced, confirmed and extended by means of modern methods (e.g. chromosome, surface antigen and immunological markers, fluorescence distribution analysis, isotope labelling, electron microscopy [20–34]).

The subcapsular, large immature lymphoblastic cells [13, 14] did not attract attention until they were redescribed in identical experimental conditions (regeneration of thymus *in situ* after X-ray involution or in regenerating syngeneic grafts) more than 20 years later ([35], see also [21, 36]). These cells were found to play a key role in immune mechanisms and in the initiation of lymphoid leukaemia. At the present time, they are intensively investigated in a rapidly increasing literature. An expanding field of study can be foreseen about the problem of the chemo-attractant properties of the epithelial cells of the thymic cortex toward the lymphocytes [37].

The first thymic active substances available in the sixties (thymosin, lymphocytopoietic factor [38]; lymphocyte stimulating factor (LSF [39, 40]; thymic humoral factor, THF [41, 42]; serum thymic factor, STF [43, 44]) were fractions or emulsions prepared from the whole normal calf thymus or from the serum of pig blood. Until then, extracts of pure epithelial components had been used in a single study [18].

The exclusive survival of the epithelial cells in thymus grafts enclosed in Millipore diffusion chambers made it possible to discover the existence in the thymic epithelium of a humoral factor capable of restoring immunological competence in lymphoid cells of neonatally thymectomized animals [41, 45, 46].

HORMONAL IMBALANCE AND THE THYMUS

Around the thirties, several endocrinologists still considered the thymus as a subsidiary organ, no more than a bag of lymphocytes, and its epithelial components left after acute accidental involution as insignificant debris. In the normal thymus, generally used for appreciating stimulating or inhibiting hormonal influences, the cortical epithelial components, overshadowed by the crowding of lymphocytes, escaped observation. On the other hand, during the first stages of regeneration of the thymus, X-irradiated under shielding of the other parts of the body, early cytological changes, poorly known at that time, in the two main components of the thymus, including the unique specific structure, the epithelial reticular cells, may easily be observed [47]. The transient phase during which the immature stem cells (lymphoblasts) appear, is also an excellent criterion for estimating rapidly acceleration or delay of regeneration.

The present survey will be limited to a summary of the reactions of the irradiated thymus to adrenalectomy [48, 49], hyperthyroidy [50–52], administration of sex hormones [53, 54] and gonadectomy [55], performed alone or combined. The changes in the mitotic index were estimated by use of the colchicine test.

ADRENALECTOMY [48, 49]

An early stimulating influence of adrenalectomy, performed 24 h after local X-irradiation, was already observed 48 h afterwards in the epithelial [49] (early appearance of mitoses) and in the lymphoid elements [48] (early appearance of lymphoblasts in the epithelial reticulum, rapid mitotic proliferation of these cells into medium-sized lymphocytes). During the following days, the cinetic index remained higher in epithelial and lymphoid cells than in the sham-operated controls. The results indicated the existence of a specific moderating influence, not yet reported at that time, of the adrenal glands on the epithelial components of the thymus cortex.

EXPERIMENTAL HYPERTHYROIDY [50, 51]

A hypertrophy of the thyroid gland reaching four to seven times the average normal weight, with histological signs of intense hyperactivity, produced by thyrotropic hormone, did not lead in chicks to decrease of the weights of thymus and bursa fabricius, as long as the treatment was not accompanied by loss in body weight and delay in the growth of the animals. A negative metabolic balance produced rapidly involutive changes in the organs. In view of this inert reaction of the normal thymus toward an intense functional thyroid hyperplasy, the treatment was tested on the regeneration of the X-ray irradiated thymus. In immature rats and guinea pigs, injection of considerable amounts of thyroxin had little influence on thymus regeneration, provided that the treatment did not induce growth alteration of the animals. The intense hyperactivity of the thyroid gland produced by thyrotropic hormone led to a slight acceleration of cortical regeneration in the thymus of rats and of guinea pigs and an intense acceleration in chicks.

In Grave's disease, hyperplasy of thymus and of lymphoid tissues frequently coincides with a deep cachexy and with gonadal and adrenal deficiency. These combined factors were tested on regeneration of X-irradiated thymus [52] in four groups of rats after (1) gonadectomy, (2) gonadectomy and injection of high amounts of thyrotropic hormone, (3) gonadectomy and adrenalectomy, (4) gonadectomy, adrenalectomy and injection of thyrotropic hormone. An increase in the rate of acceleration of thymus regeneration and also in hypertrophy of several groups of lymph nodes occurred from group 1 to group 4, in spite of cachectic symptoms, and reflected the hyperplasy of the organ observed in Grave's disease. This experiment seemed to show that the functional deficiency of the adrenals is an important factor neutralizing the thymodepressing effects of the disease and inducing thymic and lymphoid hyperplastic changes. The results showed also that adrenalectomy potentiates the hyperplastic effects of a same amount of thyrotropic hormone in the thyroid gland of gonadectomized animals.

In attempts at chemical thyroidectomy, amino-2-thiazol [53] produced a three-fold increase in the weight of thyroidea, with intense cytological signs of hyperactivity, coinciding with an intense hypofunctional state. The treatment did not bring about loss in body weight and interfered but little with animal growth. Thymus weights were about half those of the controls.

SEX HORMONES

In the amounts used in one study [54], testosterone propionate selectively damaged the cells of the cortical epithelial reticulum. Degenerated epithelial phagocytes stuffed with lipidic inclusions (cholesterol, cholesterids) still filled the cortical zone when they had nearly disappeared from the control organ. Mitoses were absent during several days. Gaps of disintegration in the reticulum were not replaced by proliferation of surviving cells. As a repercussion of these epithelial alterations, homogeneous recolonization of the outer cortical zone was inhibited or occurred in the form of small clusters of lymphocytes—and among them lymphoblasts—near intact epithelial cells, in the median and perimedullar zones of the cortex. The mitotic index of the lymphocytes in these clusters and that in the lymph nodes draining the areas of injection of the hormone were paradoxically not reduced and even higher than in the lymphocyte cortical population in the controls. In various parts of the cortical zone of the injected animals, significant positive correlations were recorded between the cinetic index of epithelial cells and the cinetic index and density in the lymphocyte population [55]. The failure of homogeneous recolonization of the cortex by lymphocytes, in spite of the maintenance of a mitotic activity in these cells and in the lymphatic tissue of the lymph nodes, did not result from a direct influence of the hormone, but from deterioration of the epithelial cell in the vicinity of these clusters of lymphocytes. The results suggested that in physiological conditions, the gonads have a moderating influence on the thymic epithelial reticulum and then control indirectly the formation of lymphoblasts and their proliferation. Under these conditions, gonadectomy must eliminate this gonadal inhibition of the epithelial reticulum and simultaneously stimulate the appearance of lymphoblasts and their further proliferation, finally inducing thymus hyperplasy. This interpretation has been experimentally supported: in animals irradiated 49 days following gonadectomy or cryptorchidy [56], an increase in the cinetic index of epithelial cells and higher proportions of large stem cells (lymphoblasts) in the cortex indicated a distinct stimulating influence on regeneration.

From all these examples of thymus reaction to modifications of the hormonal imbalance, general conclusion was drawn that in physiological conditions, the cells of the epithelial reticulum of the thymus cortex, the unique specific element of the organ, are under hormonal control and influence the potentialities of the lymphoid populations intermingled with them.

In closing this survey, two observations made fifty years ago, and not understood at that time, might now receive a plausible explanation. In the early stages after local X-irradiation of the rabbit thymus [57], groups of pycnotic thymocytes alternated in the cortical zone ([57]: speckled or 'starsky' aspect) with groups of intact thymocytes associated with one epithelial nucleus, and encircled in part by a membrane. The second observation concerned the small groups of lymphocytes reported above, significantly clustered around individual epithelial cells in the cortical region of irradiated thymus in animals injected with testosterone propionate.

In both cases, these associations between lymphocytes and epithelial cells correspond to true 'thymic nurse cells' (TNC) [58, 59] and their enclosed elements. In the 1934 paper [57], Figs. 3 and 4 obviously show TNC, unrecognized at that time.

REFERENCES

1. Maximow A. Untersuchungen über Blut und Bindegewebe II. Ueber die Histogenese der Thymus bei Saügetieren. *Arch Mikr Anat* 1909, **74**, 525.
2. Maximow A. IV Ueber die Histogenese der Thymus bei Amphibien. *Arch Mikr Anat* 1912, **79**, 560–611.
3. Maximow A. V Ueber die embryonale Entwicklung der Thymus bei Selachiern. *Arch Mikr Anat* 1912, **80**, 39–88.
4. Jolly J. La bourse de Fabricius et les organes lympho-épithéliaux. *Arch Anat Micr* 1914, **16**, 363–542.
5. Stöhr Ph. Uber die Natur der kleinen Thymuszellen. *Anat Hefte* 1906, **31**, 409–457.
6. Dustin AP. Recherches d'histologie normale et expérimentale sur le thymus des Amphibiens anoures. *Arch Biol* 1920, **30**, 601–690.
7. Hammar JA. Zur Histogenese und Involution der Thymusdrüse. *Anat Anz* 1905, **27**, 23–30, 41–80.
8. Heineke H. Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf innere Organe. *Mitt Grenzgeb Med Chir* 1905, **14**, 21–94.
9. Rudberg H. Studien über die Thymusinvolution I. Die Involution nach Röntgenbestrahlung. *Arch Anat Physiol* (Anat Suppl), 1907, 123–174.
10. Regaud Cl, Crémieu R. Sur l'involution du thymus produite par les rayons X. Résultats expérimentaux. Déductions thérapeutiques. *Lyon Méd* 1912, **118**, 1–18.
11. Tschassownikow N. Einige Daten zur Frage von der Struktur der Thymusdrüse auf Grund experimenteller Forschungen. Gewebezüchtung *in Vitro*, Röntgenbestrahlung, Vitalfärbung mit Lithion Karmin. *Zeitschr Zellfg mikr Anat* 1929, **8**, 251–295.
12. Grégoire Ch. Contribution expérimentale à l'étude du thymus des mammifères. L'action comparée des rayons X sur le thymus au cours de l'histogenèse et chez l'adulte, envisagée spécialement au point de vue de la radiosensibilité des petites cellules thymiques, de la nature du processus de phagocytose et du mécanisme de la régénération. *Arch Intern Méd Expér* 1932, **7**, 513–629.
13. Grégoire Ch. Recherches sur la symbiose lymphoépithéliale au niveau du thymus de mammifère. *Arch Biol* 1935, **46**, 717–820.
14. Grégoire Ch. Uber das Verhalten des Lymphocyts bei der lympho-epithelialen Symbiose in der Thymus. *Virchows Arch pathol Anat Physiol* 1939, **303**, 457–480.
15. Jolly J, Lieure C. Recherches sur la greffe du thymus. Phénomènes histologiques de la reconstitution du thymus greffé. *Arch Anat Micro* 1932, **28**, 159–221.
16. Popoff NW. The histogenesis of the thymus as shown by tissue cultures, transplantation and regeneration. *Proc Soc Exp Biol* 1926, **24**, 148–151.
17. Hartmann A. Die Entwicklung der Thymus beim Kaninchen. *Arch Mikr Anat* 1915, **86**, 69–112.
18. Grégoire Ch, Duchâteau Gh. A study on lympho-epithelial symbiosis in thymus. Reactions of the lymphatic tissue to extracts and to implants of epithelial components of thymus. *Arch Biol* 1956, **67**, 269.
19. Grégoire Ch. The cultivation in the living organism of the thymus epithelium of the guinea-pig and rat. *Q J Microsc Sc* 1958, **99**, 511–515.

20. Law LW, Miller JH. The influence of thymectomy on the incidence of carcinogen-induced leukemia in strain D BA mice. *J Natl Cancer Inst* 1950, **11**, 425–437.
21. Carnes WH, Kaplan HS, Brown MB, Hirsch BB. Indirect induction of lymphomas in irradiated mice III. Role of the thymic graft. *Cancer Res* 1956, **16**, 439–433.
22. Law LW. Increase in incidence of leukemia in hybrid mice bearing thymic transplants from a high leukemic strain. *J Natl Cancer Inst* 1952, **12**, 789–805.
23. Metcalf D, Sparrow N, Nakamura K, Ishidate M. The behaviour of thymus grafts in high and low leukemia strains of mice. *Austr J Exp Biol Med Sci* 1961, **39**, 441–454.
24. Miller JFAP. Role of the thymus in virus-induced leukaemia. In: Wolstenholme GEW, Connor MO, eds. *Tumour Viruses of Murine Origin.* Ciba Foundation Symposium. London, Churchill, 1962, 262.
25. Ford CE, Micklem HS. The thymus and lymph nodes in radiation chimeras. *Lancet* 1963, **1**, 359–362.
26. Wakonig-Vaartaja R, Metcalf D. The origin of mitotic cells in normal thymic grafts. *Lancet* 1963, **1**, 1302.
27. Harris JE, Ford CE. Cellular traffic of the thymus: experiments with chromosome-markers. Evidence that the thymus plays an instructional part. *Nature* 1964, **201**, 884.
28. Metcalf D, Wakonig-Vaartaja R. Stem cell replacement in normal thymus grafts. *Proc Soc Exp Biol Med* 1964, *115*, 731.
29. Dukor P, Miller JFAP, House W, Allman V. Regeneration of thymus grafts I. Histological and cytological aspects. *Transplantation* 1965, **3**, 639–668.
30. Blackburn WR, Miller JFAP. Electron microscopic studies of thymus graft regeneration and rejection I. Syngeneic grafts. *Lab Invest* 1967, **16**, 66–83.
31. Blackburn WR, Miller JFAP. Electron microscopic studies of thymus graft regeneration and rejection II. Syngeneic irradiated grafts. *Lab Invest* 1967, **16**, 833–846.
32. Hays EF. The effects of allografts of thymic epithelial reticular cells on the lymphoid tissues of neonatally thymectomized mice. *Blood* 1967, **29**, 30–40.
33. Mandel T, Russell PJ. Differentiation of foetal mouse thymus. Ultrastructure of organ cultures and of subcapsular grafts. *Immunology* 1971, **21**, 659–674.
34. Miller JFAP. Lymphocyte interactions in antibody response. *Int Rev Cytol* 1972, **33**, 77–125.
35. Kaplan HS. The role of cell differentiation as a determinant of susceptibility to virus carcinogenesis. *Cancer Res* 1961, 981–983.
36. Miller JFAP. Immunological significance of the thymus of the adult mouse. *Nature* 1962, **195**, 1318–9.
37. Le Douarin NM. Cell migrations in embryos. *Cell* 1984, **38**, 353–360.
38. Roberts S, White A. Biochemical characterization of lymphoid tissue proteins. *J Biol Chem* 1949, **178**, 151–162.
39. Metcalf D. The thymic origin of the plasma lymphocytosis stimulating factor. *Br J Cancer* 1956, **10**, 442–457.
40. Metcalf D. The thymus lymphocytosis stimulating factor. *Ann NY Acad Sci* 1958, **73**, 113.
41. Levey RH, Trainin N, Law LW. Evidence for function of thymic tissue in diffusion chambers implanted in neonatally thymectomized mice. Preliminary report. *J Natl Cancer Inst* 1963, **31**, 199–217.
42. Trainin N. Thymic hormones and the immune responses. *Physiol Rev* 1974, **54**, 272–315.
43. Bach JF, Dardenne M. Thymus dependency of rosette forming cells. Evidence for a circulating thymic hormone. *Transpl Proc* 1972, **4**, 345.
44. Bach JF, Dardenne M. Studies on thymic products II. Demonstration and characterization of a circulating thymic hormone. *Immunology* 1973, **25**, 353.
45. Osoba D, Miller JFAP. Evidence for humoral thymus factor responsible for the maturation of immunological faculty. *Nature* 1963, **199**, 653–654.
46. Osoba D, Miller JFAP. The lymphoid tissues and immune responses of neonatally thymectomized mice bearing thymus tissue in Millipore diffusion chambers. *J Exp Med* 1964, **119**, 177–194.
47. Grégoire Ch. Détection rapide d'un effet LC-excitateur au niveau du thymus: adrénalectomie et régénération du thymus après involution aigüe. *CR Soc Biol* 1940, **134**, 271–273.
48. Grégoire Ch. Recherches sur les relations entre thymus et surrénales II. Les réactions des cellules du reticulum épithélial thymique à l'ablation des surrénales. *Arch Int Pharmacod Thér* 1942, **67**, 446–465.
49. Grégoire Ch. Regeneration of the involuted thymus after adrenalectomy. *J Morphol* 1943, **72**, 239–261.
50. Grégoire Ch. Influence de l'hormone thyréotrope anté-hypophysaire sur les organes lympho-épithéliaux de l'oiseau (thymus, bourse de Fabricius). *Arch Int Pharmacod* 1941, **65**, 32–51, 393–406.
51. Grégoire Ch. Influence de l'hyperthyroïdie expérimentale (thyroxine, hormone thyréotrope anté-hypophysaire) sur la régénération du thymus consécutive à une involution aigüe. *Arch Int Pharmacod Ther* 1942, **67**, 173–229.
52. Grégoire Ch. Recherches sur les facteurs de l'hyperplasie du thymus et du tissu lymphoide dans la maladie de Basedow. *Arch Int Pharmacod* 1942, **68**, 263–296.

53. Grégoire Ch. Goitrogenic effect of aminothiazole and reactions of thymus and lymphoid tissue. *J Endocr* 1949, **6**, 14–22.
54. Grégoire Ch. Sur le mécanisme de l'atrophie thymique déclenchée par les hormones sexuelles. *Arch Int Pharmacod Thér* 1945, **70**, 45–77.
55. Bourgeois P, Coutrez R, Grégoire Ch. Calcul de certaines corrélations entre les cellules de la charpente épithéliale et les cellules lymphoïdes de l'écorce thymique dans certaines conditions expérimentales. *Arch Int Pharmacod Thér* 1945, **70**, 401–410.
56. Grégoire Ch. Sur le mécanisme de l'hypertrophie thymique déclenchée par la castration. *Arch Int Pharmacod Thér* 1945, **71**, 147–163.
57. Grégoire PE, Grégoire Ch. Elimination de l'acide nucléinique du thymus après involution aigüe produite par les rayons X. *Arch Int Méd Exp* 1934, **9**, 283–316.
58. Wekerle H, Ketelsen UP. Thymic nurse-cells. Ia-bearing epithelium involved in T-lymphocyte differentiation. *Nature* 1980, **283**, 402–404.
59. Werkele H, Ernst M. Thymic nurse-cells. Lympho-epithelial cell complexes in murine thymuses: morphological and serological characterization. *J Exp Med* 1980, **151**, 925–944.