106. Yu AL, Gillies SD, Reisfeld RA. Phase I clinical trial of CH14.18 in patients with refractory neuroblastoma [Abstract]. *Proceedings of the American Society of Clinical Oncology* 1991, **10**, 318.
107. Gaze MN, Wheldon TE, O'Donoghue JA, *et al.* Multi-modality megatherapy with [131I]meta-iodobenzylguanidine, high dose melphalan and total body irradiation with bone marrow rescue: feasibility study of a new strategy for advanced neuroblastoma. *European Journal of Cancer* 1995, **31A**, 252–256.
108. Pardo N, Marti F, Fraga G, *et al.* High-dose systemic interleukin-2 therapy in stage IV neuroblastoma for one year after autologous bone marrow transplantation: pilot study. *Medical and Pediatric Oncology* 1996, **27**.
109. Donfrancesco A, Deb G, Dominici C, Pileggi D, Castello MA, Helson L. Effects of a single course of deferoxamine in neuroblastoma patients. *Cancer Research* 1990, **50**, 4929–4931.
110. Liu L, Wang J. *Biochemistry of DNA topoisomerases and their poisons*. New York, Oxford Press, 1991.
111. Brodeur GM, Nakagawara A. Molecular basis of clinical heterogeneity in neuroblastoma. *American Journal of Pediatric Hematology/Oncology* 1992, **14**, 111–116.

Acknowledgements—This work was supported in part by grant CA-25408 from the National Cancer Institute and a grant from C.R.A.Y.O.N. (Cancer Research and Youth Outreach Network).

PII: S0959-8049(97)00308-0

Commentary

F. Berthold

Children's hospital, University of Cologne, Joseph Stelzmann Strasse 9, 50924 Cologne, Germany

FOR MORE than 130 years physicians have been aware of a tumorous disease called 'neuroblastoma', which may prove to be not only a malignant tumour, but also an embryonal remnant. In 1864, Rudolf Virchow was the first person to describe a child with an abdominal tumour with predominant microscopic features of a glioma [1]. The gliomatous aspect of neuroblastoma has been neglected for more than a century, but is now considered the reactive, stromal component of the tumour. This idea came from the observation that Schwann cells did not show the molecular abnormalities found in the neuroblasts and appear to play a key role in the process of maturation from neuroblastoma to ganglioneuroblastoma and to ganglioneuroma [2].

As summarised in R.P. Castleberry's excellent update, the detection of numerous molecular characteristic has considerably increased our ability to discriminate between neuroblastoma with a good or poor prognosis. This was possible by the close association of factors such as MYCN amplification, loss of heterozygosity on chromosome 1p36.2→ter, DNA euploidy, loss of CD44 or trkA expression and others with stage and outcome. MYCN proved to be the most powerful single prognostic factor in most series, reliably predicting poor outcome in nearly all amplified cases. A low risk group with MYCN amplification in stage 2A/2B ≥ 1 to 21 years of age, a composite of criteria from the Childrens' Cancer Study Group and the Pediatric Oncology Group (see Table 3 of the Update) would therefore not be accepted universally. The molecular factors are certainly not independent from each other (e.g. MYCN and LOH 1p and nonexpression of CD44 are correlated). They predict the outcome of a fraction of a defined group only (e.g. MYCN amplification in 30% of all stage 4 neuroblastoma experiencing an 80% death rate) and therefore require the addition of clinical risk factors, such as stage, age, serum LDH (lactate dehydrogenase) level, platelet count and others [3]. Furthermore, their specific roles in oncogenesis and function at the cellular level are hardly understood, but might be a prerequisite in order to understand and manipulate regression, maturation or progression in neuroblastoma cells.

Regression is a common feature of the embryofetal life including the development of the sympathetic system. The adrenal gland, for example, presents at week 12 and is the same size as the kidney, but it regresses during fetal and infant development until it is a small gland. Similarly the Zuckerkandl's ganglion at the origin of the A.mes.sup. appears as a large paired organ at gestational week 8. The cells of embryonal paraganglia resemble and appear indistinguishable from the neuroblasts of neuroblastoma. Thus, spontaneous regression of stage 4S neuroblastoma may be comparable to the regressive process of the Zuckerkandl and other paraganglia.

Since patients with microscopic residual stage 1 disease have a survival rate close to 100% without cytotoxic therapy, these *in situ* residual cells presumably also undergo regression. Kushner and associates recently reported on 2 patients with recurrent or enlarging tumours which regressed spontaneously [4]. In our series, 8 patients with Evans' stage III neuroblastoma who did not receive chemo- or radiotherapy to treat the residual disease, survived for 4–14 years suggesting some level of spontaneously remission. Seven of the 8 patients were infants at diagnosis. Finally, the 2.7 fold increased standardised incidence ratio of neuroblastoma in screening areas compared with regions without screening reflects the detection of cases which would otherwise have gone undetected but would have spontaneously regressed (in the absence of screening). This leads to the hypothesis that neuroblastoma may represent an embryonal remnant and a malignant tumour. The embryonal residuum predominantly presents early in life (stages $4S > 1–3 \gg 4$) *and* has the ability to spontaneously regress. The malignant tumour appears later ($4 \gg 1–3 > 4S$) and shows characteristically progression (Figure 1).

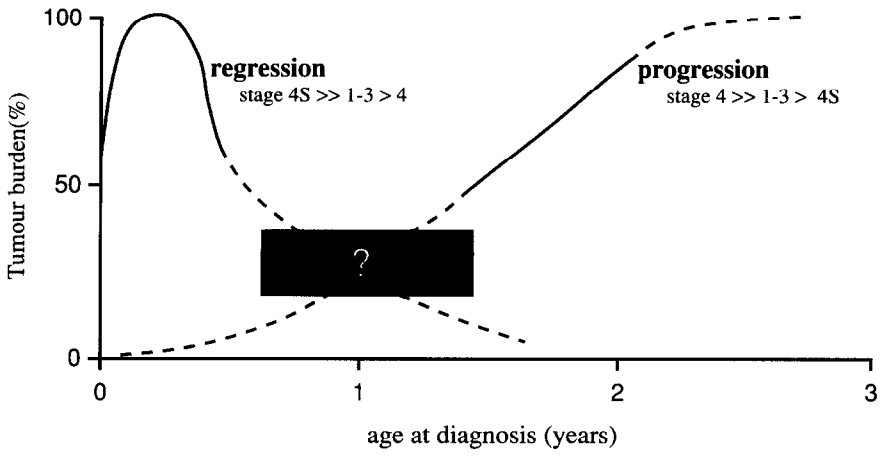

Fig. 1. Hypothetical scheme of the time course of regression and progression in children with neuroblastoma.

Whether or not an intermediate type of neuroblastoma (see Table 2 of the update) really exists as an entity is currently unproven. Approximately half the patients presenting with recurrences from stage 1–3 disease show distant metastases at the time of relapse [6], but it is still unknown whether the malignant type evolves consistently and, in the majority of cases, from the benign phenotype.The International neuroblastoma staging system (INSS) is accepted as currently the best available by major national groups. However, it is still to be proven, for example, that the discrimination of stages 2A versus 3, or stage 1 with adhering lymph nodes versus 2B, is really of prognostic significance. Another example is the borderline between stage 4 in infancy and stage 4S. Strict adherence to the definition would result in classifying larger primary tumors (> 2A/B) or lymph node involvement beyond regional as stage 4 with the implementation of cytotoxic therapy. Experience from several countries suggests that it is worthwhile waiting for spontaneous regression in those patients. International working parties to study all available data on the INSS classification and to reach agreement are underway.

1. Virchow R. Hyperplasie der Zirbel und der Nebenniere. In Hirschwald A. *Die krankhaften Geschwülste Vol. 2.* Berlin, 18. Vorlesung, 7.2, 1863, 148–150.
2. Ambros IM, Zellner A, Poald B, Amann G, Ladenstein R, Printz D, Gadner H, Ambros PF. Role of ploidy, chromosome 1p, and Schwann cells in the maturation of neuroblastoma. *N Engl J Med* 1995, **334**, 1505–1511.
3. Christiansen H, Sahin K, Berthold F, Hero B, Terpe HJ, Lampert F. Comparison of DNA aneuploidy, chromosome 1 abnormalities, MYCN amplification and CD44 expression as prognostic factors in neuroblastoma. *Eur J Cancer* 1995, **31A**, 541–544.
4. Kushner BH, Cheung N-K, LaQuaglia MP, Ambros PF, Ambros IM, Bonillac MA, Gerald WL, Ladanyi M, Rosenflield NS, Yeh SDJ. Survival from locally invasive or widespread neuroblastoma without cytotoxic therapy. *J Clin Oncol* 1980, **14**, 373–381.
5. Woods WG, Tuchman M, Robison LL, Bernstein M, Leclerc J-M, Brisson LC, Brossard J, Hill G, Shuster J, Luepker R, Byrne T, Weitzman S, Bunin G, Lemieux B. A population-based study of the usefulness of screening for neuroblastoma. *Lancet* 1980, **348**, 1682–1687.
6. Berthold F, Hero B, Breu H, Christiansen H, Erttmann R, Gnekow A, Herrmann F, Klingebiel T, Lampert F, Müller-Weihrich S, Weinel P. The recurrence patterns of stages I, II and III neuroblastoma: experience with 77 relapsing patients. *Ann Oncol* 1992, 7, 183–187.