Publisher's Note

This month sees publication of the first issue of the *European Journal of Cancer* under its new Editor in Chief, Professor Michael Peckham. With his guidance and that of his fellow Editors, and with the support of four of Europe's leading cancer organizations, the Journal has been redesigned to meet the changing needs of research and clinical specialists in cancer over the next decade and beyond.

Robert Maxwell
Publisher

Professor Henri Tagnon

WITH great foresight Professor Tagnon founded the *European Journal of Cancer and Clinical Oncology* 25 years ago, so providing the basis for many of the important developments in European cancer medicine and research as well as for the new *European Journal of Cancer*. His career is a distinguished one; he was Professor of Medicine and Oncology at the Université Libre de Bruxelles from 1965 to 1976 and from 1953 to 1976 was Chief of Medicine and Clinical Investigation at the Institut Jules Bordet. Henri Tagnon formed a valuable bridge between American and European Medicine having worked in the United States from 1940 to 1953 at Cornell, Harvard, the Sloane Kettering Institute and Memorial Hospital.

He has been intimately associated with the development of the EORTC since its inception in 1963, becoming President from 1974 to 1978. He has also been Chairman of the Advisory Board of the European School of Oncology. As founding Editor in Chief of the *European Journal of Cancer and Clinical Oncology* and having spent his professional life fostering the interaction between basic science and clinical oncology and striving to strengthen European activities in the cancer field, we hope that Professor Tagnon will derive great pleasure from the future evolution of the *European Journal of Cancer* and we thank him warmly for his consistent leadership over many years.

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Eur J Cancer, Vol. 26, No. 4, pp. 417–419, 1990.
Printed in Great Britain

0277-5379/90$3.00 + 0.00
Pergamon Press plc

Suramin: a New Therapeutic Concept

SURAMIN, which was first synthesized in 1917, has been used as a chemotherapeutic agent since 1924 following work at the Institute Pastur [1] which led to its use as a trypanocidal drug. It remains the drug of choice for onchocerchiasis. A recent letter to the editor of the *JNCI* [2] gave suramin an interesting historical perspective, by linking it to anionic dyes and to the father of chemotherapy, Paul Ehrlich. It has also been related to polyanionic glycosaminoglycans and heparinoids, with their biochemical, biological and pharmacological properties. Suramin was found in 1979 to be a reverse transcriptase inhibitor [3] and subsequent *in vitro* work showing HIV replication inhibition [4] provided the basis for clinical observations [5] of reduced viraemia in AIDS patients. This led to controlled trials in AIDS that proved to be negative [6, 7]. Following documentation of a complete clinical response in a patient with Kaposi's sarcoma and non-Hodgkin lymphoma [7], Stein, LaRocca and Myers at the NCI made a low key but determined effort to retain interest in the drug as a potential anticancer agent. Most of the information on suramin in cancer treatment, including its toxicity, comes from their reported and published experience. These efforts have excited the interest of medical oncologists and raised the possibility of a new type of anticancer treatment. In 1989, Stein and colleagues [8] reported their experience of treating a group of patients with renal cancer, adreno-carcinoma and lymphoma. The results obtained in adrenocortical carcinoma were interesting and have subsequently been confirmed [9, 10]. The rationale of using the drug in this setting was based on the toxic effects of suramin, which causes adrenal insufficiency [11].

The Myers group looked for other diseases in which suramin might be active, given the action of the drug on most known growth factors. The presence of basic FGF in prostate cancer tissue [12] prompted them to investigate suramin in this condition. Early encouraging results were reported at the NCI-EORTC [13], and the ASCO [14] meetings last year. The article by Van Oosterom and colleagues in the present issue of *EJC* [15] is the first prospective European study of suramin in the treatment of cancers, other than adrenocortical carcinoma. Their previous biochemical and pharmacological work provides a firm basis for the clinical study [16]. The brevity of the report does not detract from its significance. Although the activity of suramin in prostate cancer is shortlived and mainly biochemical, it is encouraging evidence of the development of a new approach to cancer therapy. The authors describe the differences between their dose levels and those employed by the NCI group; this difference might explain the results observed. The modest results obtained in the European study warn against excessively optimistic expectations generated by initial experience.

In parallel with clinical studies of its antitumour effects, the biological activity of suramin as an inhibitor of growth factor activated phenomena has also been studied [17, 18]. The effects were so striking and reproducible that suramin has been used for the past 5 years as a laboratory tool in embryology, and in developmental and oncological neurology. The study of its biological effects has been greatly expanded. Its purported range of activity includes inhibition of anaerobic glycolysis [19], inhibition of protein kinase C [20], and the reversal of *in vitro* growth factor mediated oncogene induced transformation [21,

22]. It is a well known inhibitor of DNA polymerases, reverse transcriptase as well as many other enzymatic systems [3, 23]. Suramin also induces *in vitro* differentiation in several models [19, 20, 24]. Its antimitogenic properties are linked to growth factor binding inhibition [17, 18, 23, 25–27]. It also acts on cell mediated cytotoxic models [28].

Suramin also interferes with the binding of growth factors which inhibit proliferation and growth, and it could hypothetically lead to tumour growth enhancement [29]. Its antiproliferative effects are potentiated by steroids in several models [26, 30].

Growth factor dependent tumour progression has been linked to both autocrine and paracrine mechanisms, and the stromal and neoangiogenic paracrine loops determining tumour progression, are one of the most active areas of tumour biology. The potential role of suramin for this aspect of tumour growth was explored in several posters at the last ASCO/AACR meeting [31, 32]. As a result of this work there has been considerable interest in the development of structural or functional analogues of suramin [33], with the same growth factor triggered tumour growth inhibition profile.

On a cautionary note, the pharmacokinetic profile of suramin, with one of the longest recorded half-lives [16, 34], and the apparent plasma level/activity and toxicity relationships of the drug [8, 14, 35] need to be taken into account in therapeutic planning and in the eventual association of the drug with other agents, whether hormonal or cytostatic. Polyanionic molecules that are not metabolized are likely to have the same profile, since they will 'stick' to everything and are not likely to be excreted rapidly in the urine or faeces.

The action of suramin on tumours is likely to be cytostatic or apoptotic rather than cytocidal, and its potential role in adjuvant treatment or as maintenance therapy following hormone or cytostatic drug induced responses, can easily be envisaged.

The eventual association of suramin with other agents needs to be considered early in the development of its clinical use as suggested by the findings of Berns and colleagues [36] reported in this issue. The paper follows their recent abstract at Dusseldorf [37]. Hormone dependent growth of both cancer and non-cancer cell lines was inhibited by suramin. Its significance has theoretical implications. It is clearly shown that this effect is mediated through growth factors, and that in hormonally induced, EGF mediated growth, suramin has concentration dependent and reversible differential effects. Berthois and Martin have recently reported similar experiments using the hormono-dependent breast cancer MCF-7 line [38]. In both studies suramin appeared to have a reversible effect. It is possible that the concomitant or sequential association with hormonal manipulation may reverse resistance to hormonal therapy or potentiate the sensitivity to hormones, or to their deprivation.

The association of suramin with steroids is another area of interest. Studies using *in vitro* models have shown that the level of suramin needed for growth inhibition decreases when steroids are added [26, 30].

The toxicological profile of suramin is complex, and the drug can cause serious problems. Low grade fever, keratopathy [39], skin rash, leuko- and lymphopenia [8], severe neurotoxicity, kidney toxicity, liver dysfunction, adrenal insufficiency [8] and coagulation problems [40] have been described. Suramin induced glycosaminoglycan turnover perturbations have been used to create animal models of human disease [41], and are at the origin of many of the toxic problems, such as coagulation and keratopathy; while high levels of concentration of the drug in the adrenal gland, liver and kidney are associated with organ specific toxicity [11]. Neurological toxicity, the major cause of concern [42], is believed to be due to the effect of suramin on basic FGF, an essential homeostatic substrate for healthy Schwann cells. New toxic side effects are probable and need to be identified with careful attention.

The clinical development of suramin may have a comparable significance to the development of aminopterin or nitrogen mustard, by providing a new and unique therapeutic prospective. Although aminopterin has never been used, and nitrogen mustard is employed only in the MOPP combination, their clinical development gave birth to cancer chemotherapy.

Today, medical oncologists are better equipped to interact closely with basic scientists and have at their disposal improved pharmacological and clinical research methodology. A challenge for medical oncology is to incorporate agents such as suramin which act on growth control mechanisms into the therapeutic arsenal.

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Eur J Cancer, Vol. 26, No. 4, pp. 419–420, 1990.
Printed in Great Britain

0277-5379/90$3.00 + 0.00

Early Presentation of Results in Clinical Trials: an Ethical Dilemma for Medicine and Science

The paper 'Adjuvant chemotherapy for medulloblastoma, the first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I)', by Tait *et al.* [1], is intriguing and contains several aspects of interest. In the trial, the value of adjuvant chemotherapy was tested in patients receiving radiotherapy for medulloblastoma. The results published in the paper, which appears in the present issue, demonstrate that even for rare tumours, clinical trials can answer relevant questions only through the cooperation of multidisciplinary teams in many centres. The outcome of such a trial, because of its multicentre character, has much wider applicability than results obtained in a single institution. Another interesting aspect of the study is a significant difference in treatment outcome between the large and small centres in favour of the former (56.9 vs. 41.8% 5 year disease-free survival respectively; $P < 0.005$). Such a difference in survival may be the result of differences in patient selection or the more extensive experience in the management of rare tumours which may require complex treatment in larger centres. Nevertheless, the results point to the need for centralization of treatment for rare tumours.

One of the most notable aspects of the trial was its termination at an early stage because it was considered unethical to deprive patients of chemotherapy in view of the significant difference in favour of combined modality treatment shown at early interim analysis. With the longer follow-up, however, the difference became smaller and lost its significance. As a result the study has not been able to determine whether the lack of a significant difference reflects insufficient sample size, ineffective chemotherapy, choice of statistical method or is due to other reasons.

In general, the premature closure of a clinical trial and publication of preliminary data may result in the following consequences:

1. A new therapeutic approach cannot be reliably assessed.
2. Unproven therapy may be adopted as standard practice leading to the use of ineffective yet potentially toxic treatment in a large number of patients outside the setting of a clinical trial.
3. In designing a new trial a suboptimal standard arm may be selected.