Cancer Chemother. Pharmacol. 1, 5–13 (1978)

Cancer Chemotherapy and Pharmacology

Short Review

New Cancer Chemotherapy Drugs in Europe

G. Mathé[1, 3] and L. M. van Putten[2, 3]

[1] Institut de Cancérologie et d'Immunogénétique, Hospital Paul-Brousse and Service d'Hématologie de l'Institut Gustave-Roussy, 94800-Villejuif, France

[2] Radiobiological Institute TNO, Rijswijk, The Netherlands

[3] EORTC

In this short review attention is drawn to promising new drugs and to promising new information on old drugs. The information may concern clinical results or pertain to preclinical data. The selection of drugs is arbitrary and no claim of completeness of listing is made. Hormones have not been considered.

Alkylating Agents

Ifosfamide. This isomeric analogue of cyclophosphamide has been further characterized. In addition to a better definition of its toxicity (Rodriguez et al., 1976), a large number of early clinical experiences have been described (EORTC Clinical Screening Group, 1975; International Holoxan Symposium, 1978). However, so far no systematic comparison of the drug with cyclophosphamide has been carried out to evaluate the relative merits of the two agents. A clinical trial for such a comparison would be highly desirable.

Other Cyclophosphamide Analogues. As a number of activation products of cyclophosphamide and their derivatives have been synthesized, additional data are becoming available on the biological activity of these products (Colvin et al., 1976; Hohorst et al., 1976). Some of them seem to be good cytostatic agents and do not need activation in the liver to become effective. So far, however, no data are available on the therapeutic usefulness of these agents.

Peptichemio, a mixture of six peptides of m-di-(2-chloro-ethyl)-amino-L-phenylalanine, was submitted to a phase II clinical trial by the EORTC Clinical Screening Group (1977c), which not only confirmed its oncostatic action described in Italy (see Astaldi, 1975), but underlined that it could induce regressions in diseases for which chemotherapy is poor today, such as neuroblastoma, uterus cervix cancer, larynx tumours, and chronic myeloid leukaemia blastic crisis. De Barbieri et al. (1977) are developing a large series of *di-(2-chloroethyl) glycopeptides,* some of which give promising results on sarcoma 180 and L1210 leukaemia.

Cyclotriphosphazatrien and derivatives (especially photrin) may be more efficient on some transplantable tumours and less toxic than previously available chemotherapy compounds, exerting their activity through ethylene-imine groups (Saphonova and Chernov, 1977).

Threosulfan, or dihydroxy-busulfan, has been shown to be remarkably effective in ovarian carcinoma (Fenelly, 1977).

Dianhydrogalactitol (NSC132313). This hexitol diepoxide was developed in Budapest (Németh et al., 1972) where its effects were studied extensively in models. Its cellular effects and phase sensitivity have been described by Pályi (1975). Pharmacokinetic studies indicated its good penetration into the brain, and its effectiveness on brain tumour models confirmed these findings (Geran et al., 1974; Levin et al., 1976). Phase I studies on i.v. treatment were performed by Eagan et al. (1976) and on oral treatment by the EORTC Early Clinical Trials Group (de Jager et al., 1977). Toxicity was limited to the haemopoietic system, and effects were noted in bronchial carcinoma (squamous and oat cell) and in G.I. tract and G.U. tract tumours.

Diacetyl dianhydrogalactitol (DADAG) is a derivative of DAG with therapeutic activity in many experimental systems (Somfai-Relle et al., 1977). The cytostatic hexitol derivatives seem to remain a fruitful area of development of our therapeutic possibilities (EORTC Screening and Pharmacology Group, 1978).

Reprint requests should be addressed to: G. Mathé

0344-5704/78/0001/0005/$ 01.80

Estramustine phosphate (Estracyt®) is a steroidal alkylating agent containing an estradiol 17β group with a nitrogen mustard covalently bound at C3.

This drug has been widely used for prostate carcinoma in Europe since its effectiveness was demonstrated in a clinical trial (Mittelman et al., 1975). Oral administration has also been found effective (Nilsson and Jönsson, 1975; Mittelman et al., 1976; Nillius and Könyves, 1976). In addition there is a suggestion that in prostatic carcinoma combination of estramustine with prednimustine may be advantageous (Mittelman et al., 1977). The rate of objective responses varies between 19 and 25%. Subjective responses were noted in a larger fraction of the patients, and side effects were limited to mild nausea and vomiting and rare gynaecomastia.

Prednimustine is a steroidal alkylating agent in which a corticosteroid (pregnadiene-dione-triol) is linked to chlorambucil. The drug has both alkylating and corticosteroid pharmacological effects (Harrap et al., 1977). It was demonstrated in phase II studies to exert effects in chronic lymphoid leukaemia (Brandt et al., 1975; Lutz et al., 1977; EORTC Clinical Screening Group, 1977a), lymphosarcoma (Möller et al., 1975; Kaufman et al., 1976), acute myeloid leukaemia (Brandt and Könyves, 1977) mammary carcinoma (Könyves et al., 1975), and melanoma (EORTC Clinical Screening Group, 1977a).

Esters of progestins and alkylating agents have been produced and studied by Hansen et al. (1977). The preliminary results of these authors on experimental tumours seem promising.

Nitrosoureas. Imbach et al. (1975) synthesized sugar derivatives of nitrosourea, among which four were shown to possess a higher oncostatic effect than CCNU and MeCCNU. They are called RFCNU, GCNU, RPCNU and XPCNU according to their sugar derivatives (respectively ribofuranosyl, glucapyranosyl, ribopyranosyl, and xylopyranosyl). Of these compounds, RFCNU may prove the most promising, as its therapeutic index is the highest of those compounds studied, and as it is not immunosuppressive at the lowest dose of the maximally efficient dose interval. Mathé et al. (1977d) obtained 30% objective regressions in a Phase II trial on digestive tract tumours. The same group (Mathé et al., 1978b) is registering a similar rate of response with RPCNU.

Fiebig et al. (1977) studied three water soluble and six bifunctional newly synthetized analogues of BCNU. The water soluble 1-(2-hydroxy-ethyl)-3-(2-chloroethyl)-3-nitrosourea showed a higher activity than BCNU in animals inoculated s.c. with Walker carcinoma, but no superiority of the new compounds compared to BCNU was found in the treatment of intracranially inoculated Walker carcinoma (Fiebig et al., 1977). The same group (Zeller et al., 1977) later compared the effect of eight new nitrosourea derivatives with BCNU on the transplantable rat leukaemia L5222. Bifunctional 1,1′-polymethylene-bis-3-(2-chloro-ethyl)-3-nitrosoureas cured a high proportion of animals carrying advanced i.p. implanted leukaemia. Out of three water soluble monofunctional alkylating 1-(hydroxyalkyl)-3-nitrosoureas, the compound 1-(2-hydroxyethyl)-3-(2-chloroethyl)-3-nitrosourea yielded more cures than BCNU and the other agents tested. It was significantly superior to BCNU against preterminal i.p. or intracranially implanted L5222 leukaemia.

Chlorozotocin or 2-[3-(2-chloroethyl)-3-nitrosoureido]-2-deoxy-D-glucopyranose, which has an alkylating activity intermediate between RPCNU and RFCNU and much superior to that of CCNU according to Schein (1977), and which produces no suppression of the peripheral neutrophils according to the group of this author (Panasci et al., 1977), was found by Mathé et al. (unpublished data) to be less toxic for colony forming units on agar.

Platinum complexes were the object of many studies. *Cis-dichloro-diammine platinum* (Cis-DDP) is evaluated in several clinical trials in Europe which confirm its efficacy at least in ovarian tumours (Wiltshaw and Carr, 1974). After Connors et al. (1972) synthetized a series of organic platinum complexes, some of which have significantly higher therapeutic indices than cis-DDP, several studies were conducted on cis-dichloro-bis-(Cyclopentylamine) platinum (DBCP) which showed that this compound, which interferes with G_1——S transition, enhances the effect of ionizing radiations in synchronizing the cells (Szumiel and Nias, 1976).

The most interesting recent compound, today, is sulfato-1,2-diamino-cyclohexane platinum, which has been shown by Hill et al. (1977) to be active in acute leukaemias and which is submitted to phase-II trials in these diseases and in other tumours which are or have become resistant to cis-dichlorodiammine platinum, as there is no cross-resistance between both compounds in mouse leukaemia (Burchenal et al., 1977).

Hexamethylmelamine water soluble analogues have been produced because of gastrointestinal side effects observed with the water insoluble preparation given by the oral route. Connors et al. (1977) have studied three derivatives with greater intrinsic water solubility: pentamethylmelamine, N-methylether derivative, and N^2,N^4, N^6-trimethylol-N^2,N^4,N^6-trimethylmelamine. They exert a strong antitumour activity on human lung tumour xenografts.

Antimetabolites

DDMP (2-4-diamino-5-(3′-5′dichlorophenyl)-6-methylpyrimidine) is a folate antagonist which was recently found to be quite effective in methotrexate resistant tumours. This effectiveness was not inhibited by the simultaneous administration of folinate (citrovorum factor, CF), which was nevertheless effective in protecting normal methotrexate sensitive tissues. Findings in tissue culture (Hill et al., 1975) had predicted this phenomenon and found its most likely explanation in the fact that most resistant cells have a decreased transport efficiency both for antifolates and for CF (Hill et al., 1977). Clinical effectiveness of the orally administered drug was demonstrated in patients with hypernephroma and lung cancer (Price et al., 1975; Calvert and Price, 1977). Further studies are in progress.

Ftorafur [(tetrahydrofuranyl-2)-5-fluorouracil]. A series of studies has been directed at analysis of the differences between 5-fluorouracil and ftorafur (Johnson et al., 1976; Garibjanian, 1976). Ftorafur was found less immunosuppressive in the mouse at equitoxic doses. The drugs differed in their spectrum of antitumour effectiveness, with 5-FU usually more effective at short periods of administration and ftorafur better tolerated in protracted treatment. Cross-resistance between 5-FU and ftorafur was shown to occur, and the most likely interpretation is that ftorafur is a slow-release form of 5-FU. The observed differences in effect and tolerance are ascribed to differences in pharmacokinetics of 5-FU and 5-FUdR released from the two drugs.

Clinical data support this interpretation. Valdivieso et al. (1976) described a clinical evaluation of the drug, and the good tolerance of the agent permitted its inclusion in combination treatment of patients who had previously been heavily treated (Buroker et al., 1977). These results confirm data from the Soviet Union and from Japan reported earlier.

Ribavirin or 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, an inhibitor of viral DNA polymerase, has been shown to reduce the incidence and/or the growth of several transplanted virus-induced tumours; unfortunately, it is strongly immunosuppressive (Newman et al., 1977).

Cystein adducts of α,β-unsaturated aldehydes (acrolein, crotonal, hydroxypentenal) have been studied by Tillian et al. (1976); they are practically nontoxic, and they exert tumour growth inhibition. It is supposed that these substances release the free aldehydes in the tumours, agents which are too toxic to be used alone, but which in the tumour cells, especially attack SH-groups which are of functional importance for DNA synthesis. The antitumour effect of 4-hydroxy-pentenal cystein adduct has been confirmed by Conroy et al. (1977).

Plant Derivatives

Podophyllotoxin derivatives prepared by Sandoz have not been disappointing after the demonstration of their oncostatic actions in humans, which were shown noticeably different for VM26 (EORTC Cooperative Group for Leukaemias and Haematosarcomas, 1972) and VP16/213 (EORTC Clinical Screening Group, 1973). They have been shown very active on metastasis in experimental models (Cattan et al., 1976). Recent research has focused on the effectiveness of VM26 on mesothelial effusions and of VP16/213 on monocytoid leukaemia (Mathé et al., 1974), on their importance in combinations studied experimentally (Dombernowsky and Nissen, 1976), and clinically, especially in lymphosarcoma (Misset et al., 1977) and gliomas (Pouillart et al., 1977).

Vinca Alkaloid Derivatives. Formyl leurosine, a modified vinca alkaloid, was introduced by Eckhardt et al. (1976), and phase I studies were reported by Farkas et al. (1976). Additional clinical studies (de Jager et al., 1977) have so far failed to reveal neurotoxicity, but were hampered by the occurrence of vasomotor reactions (hypotensive or hypertensive episodes) seen after the slow i.v. injection of the drug. After infusion over a 1-h period, these phenomena had not been observed. Activity of the drug was reported in lymphosarcomas and leukaemias. If this activity is confirmed in the absence of neurotoxicity a valuable alternative for vincristine would be available.

Vindesine, or desacetyl vinblastine amide sulfate, was the object of a phase II trial in leukaemias and lymphomas (Mathé et al., 1977c and 1978a). The authors of this trial obtained a high proportion of remissions in acute lymphoid leukaemia (ALL) and in chronic myeloid leukaemia blastic crisis, and only a few responses in lymphosarcoma and Hodgkin's disease. The most remarkable characteristic of vindesine is the absence of cross-resistance with vincristine as documented in ALL.

Ochrosia alkaloid derivatives of the *ellipticin* family have been the object of extensive studies after the demonstration of the effect on L1210 leukaemia of 9-methoxy-ellipticine (Le Men et al., 1970). *Ellipticin base* (Hayat et al., 1974), *9-hydroxy-ellipticin* (Hayat et al., 1974; Le Pecq, 1974), *9-hydroxy-2-methyl-ellipticin* and *9-hydroxy-2,6-dimethyl ellipticin* (Le Pecq et al., 1975) were shown to be active on L1210 leukaemia. Their possible neurotoxicity was demonstrated (Paoletti et al.,

1974; Pham-Huu-Chanh et al., 1974). A curious aspect of the experimental screening of 9-OH ellipticine was the phenomenon that direct drug cell contact seemed important for its activity on L1210 leukaemia (Le Pecq et al., 1976). Also for 9-OH, 2-Me-ellipticine this was found to be the case; i.p. L1210 could be cured by i.p. treatment but relapses became evident as solid tumour recurrences in the needle track (Lelieveld, 1977). In contrast, i.v. L1210 was hardly affected. This led to testing of the agent in an intra-arterial rat tumour model (Ossewaarde, 1977) in which the drug was found quite active on an epidermoid squamous carcinoma. More phase II clinical trials on methoxy-9-ellipticine have been conducted after the first one which showed a moderate effect on oligoblastic acute myeloid leukaemia (Mathé et al., 1970). More diseases are submitted to the drug and to its combination with nitrosoureas (Schwarzenberg et al., unpublished data).

Phase I–II studies by slow i.v. infusion are also presently conducted on 9-hydroxy-2-(N)-methyl ellipticine by Juret et al. (1977), who demonstrate a clearly better tolerance for this drug than predicted from the mouse (in man doses up to 100 mg/m^2 were given repeatedly without evidence of toxicity; in mice 40 mg/m^2 was about 50% lethal). In addition, some responses may be obtained in a few solid tumours. These findings suggest that drugs of this type, which, like adriamycin, bind by intercalation to DNA (Kohn et al., 1975) deserve further study.

Alangium vitiense alkaloids have been extracted by Husson et al. (1977) and shown by Mathé et al. (1977b) to be oncostatic on L1210 and P388 lymphoid leukaemias and on GC_3HED/OG Gardner lymphosarcoma. They are not active on myeloid leukaemia nor on B16 melanoma.

Other Plant Derivatives

Thirty compounds extracted from plants of the Canary Islands, almost all of which are *chromenes* or *diterpenes*, were studied for their cell respiratory inhibitory action and eventually their oncostatic active action on L1210 leukaemia. Three presented a slight effect on this neoplasia: spathelia-bis-chromene, pulverochromenol, chalepensine (Gosalves et al., 1976).

Hanerol, prepared from Chamaenerium angustifolium, which is a macromolecule belonging to the class of ellagotannins, has been shown to exert an antitumour effect on a transplantable strain of colonic adenocarcinoma (Syrkin et al., 1977).

Antibiotics and Derivatives

Adriamycin DNA complex was proposed as a more effective way of administration of adriamycin (Trouet et al., 1972, 1974). The selection of this complex was based on the concept of endocytosis as an important selective ingestion route for drugs into tumour cells. In experimental systems advantages of the complex were demonstrated in certain L1210 lines but not in others (Atassi et al., 1974, 1975; Rozencweig et al., 1975). It is quite evident that blood levels of free adriamycin are maintained longer after administration of the complex than after the free drug, and Staquet et al. (1977) showed that adriamycin-DNA complex gives higher plasma concentration than adriamycin injected alone at the same dose.

Adriamycin-protein complexes have also been studied, and protein carriers have been proposed for other drugs (Szekerte and Driscoll, 1977). The combination of the nonionic detergent *tween 80 and daunorubicin or adriamycin* markedly enhances the cytotoxic effect of these anthracyclins on several types of tumour cells (Di Marco et al., 1976). This effect could be due to selective increased uptake of the oncostatics by neoplastic cells due to changes in the membrane constitution or to an immunity adjuvant effect of tween 80. Adriamycin sensitivity was restored in an adriamycin-resistant Ehrlich ascites tumour by entrapping *adriamycin in liposomes* (Seeber et al., 1977).

Depres-De Campeneere et al. (1977) have compared L-*leucyl- and* D-*leucyldaunorubicin* (DNR). When the inoculation of both L1210 leukaemia cells and drugs was made i.p., L-leucyl-DNR was more active than DNR while D-leucyl-DNR was poorly active; when the inoculation and the treatment were given i.v., L-leucyl-DNR was less active than DNR and D-leucyl-DNR was completely inactive.

Rubidazone, or semi-synthetic benzoylhydrazone daunorubicine, has been the object of extensive clinical studies (Jacquillat et al., 1976), which showed its action in acute leukaemias especially of the monocytoid type. Chauvergne et al. (1973) did not find any significant effect on solid tumours. Maral (1977) recently showed that cardiotoxicity and immunodepressive activity of this agent is lower than those of daunorubicine. Extensive research are conducted to find new anthracyclins which would induce for the same antitumour effect less cardiotoxicity which has been shown to be related to their effect on mitochondrial functions (Bachmann et al., 1975).

Acetyldaunomycin has been shown to be able to reduce the cardiotoxic effect of adriamycin (Zbinden, 1975).

Another semi-synthetic compound, *diethoxy-acetoxy-14-daunorubicin*, has been studied experimentally by Maral et al. (1977) and shown to be more efficient on different murine tumours than daunorubicin or adriamycin at the same dose.

Demethoxydaunorubicins, characterized by the ab-

sence of the methoxyl group at the C_4-position, have been prepared by Arcamone et al. (1976) by chemical synthesis. They are 4-demethoxydaunorubicin, 4-demethoxy-7,9-diepoxydaunorubicin and their isomers. The first compound is effective against L1210 leukaemia, Gross leukaemia, and sarcoma 180 at doses four to eight times lower than those effective for daunorubicin and is active at doses 13 and eight times higher than those of its corresponding isomer. 4-demethoxy-7,9-di-epidaunorubicin and its β-isomer is devoid of any biologic activity. 4-demethoxydaunorubicine was shown effective in mice when administered orally (Di Marco et al., 1977).

Adriamycin or dioxorubicin derivatives, obtained by esterification of the 14-hydroxylic group of the saturated ring of adriamycinone, showed marked antitumour activity, generally more pronounced for compounds with an aliphatic side chain (Lenaz et al., 1974). According to Farmitalia, *adriamycin-14-octanoate* appears to be a very promising adriamycin derivative in view of its low toxicity.

N-trifluoroacetyl-adriamycin-14-valerate (AD 32) is, according to Vecchi et al. (1977) and Pratesi et al. (1978), a very efficient derivative on many murine tumours, especially more effective than other derivatives in terms of lifespan prolongation. This may be related to the fact that it is noticeably less toxic than adriamycin (Israel et al., 1975). Finally, its mechanism of action could be at least partially different from that of other adriamycin derivatives (Krishan et al., 1976).

4'-Epi-adriamycin also seems a very promising derivative, as it shows antitumour properties similar to adriamycin, but lower cardiotoxicity (Casazza et al., 1977).

Carminomycine is a new USSR antibiotic which in pilot studies was very similar in effectiveness to adriamycin. It is the subject of phase II and phase III studies as well as of a study of combination with dibromodulcitol (CMEA studies, 1977).

Aclacinomycin, a new antibiotic isolated from streptomyces galilaeus (Oki et al., 1975), belonging to the anthracyclin family, is the object of a phase II trial conducted at Villejuif, some preliminary observations of which are promising: it does not induce alopecia; it has already been shown to be active on lymphosarcoma, acute lymphoid leukaemia and chronic myeloid leukaemia blastic crisis (Mathé et al., unpublished data).

Nocamycin, produced by Nocardiopsis syringae, has been shown to exert antitumour activity (Brazhnikova and Konstantinova, 1977).

Various

ICRF159 (1,2-di-(3,5-dioxopiperazin-1-yl)-propane). This agent has been reported to have: antimetastatic activity, synergism with other cytostatic drugs (notably adriamycine), effects as a radiosensitizer as well as cytostatic effects of its own. The latter was clinically seen mainly in lymphomas and sarcomas, but also in colorectal and head and neck carcinoma. Since the excellent review by Bakowski (1976) the data on clinical applicability have not undergone major alterations. The most notable new aspect of this drug is the finding at the cellular level (Taylor et al., 1977) that it induces DNA duplication while blocking nuclear division, thus leading to polyploidy. This finding points to the necessity of considering the therapeutic possibilities of ICRF159 in a new light. Elucidation of the mechanism of action may offer the prospect of a better directed application of this drug.

Cytembena has been the object of an EORTC Clinical Screening Group (1977b) phase II trial. This trial revealed that this compound, which is sodium cis-β-4-methoxybenzoyl-β-bromoacrylate and which is not myelotoxic, is effective and able to induce regressions in uterus cervix carcinoma, a tumour against which chemotherapy was very poor.

Hycanthone has been recently reevaluated by Lelieveld (1977), who demonstrated the contrast between its toxicity for L1210 leukaemia cells and its absence of toxicity on bone marrow stem cells.

Metronidazole, which is not a 'new drug' as it has been shown to be an antiflagellate and, in addition, a radiosensitizer (Begg et al., 1974), was recently shown by Foster et al. (1976) to be directly cytotoxic for hypoxic cells.

Misonidazole (Ro-07-0582), a drug developed for radiosensitization of hypoxic cells in tumours was reviewed by Fowler et al. (1976). Drugs of this type and many newly developed congeners are reduced enzymatically under anaerobic conditions by many cell types to toxic compounds that can diffuse from the hypoxic areas in tumours and exert their cytotoxic effects also on surrounding oxygenated cells (Data of Baserga et al.; Stratford et al.; Sutherland; Olive and Durand; Brown and Yu; Denekamp [see Wardman and Adams, 1978]).

Hydrazine sulfate was able to induce partial remissions in Hodgkin's disease in a Russian trial (Gershanovic et al., 1976).

1,2-bis-diazo-acetyl-ethane has been shown, among several diazoketones studies in Moscow, as the most efficient compound of this series for antimurine leukaemia effect (Emanuel et al., 1976).

3,6-diamino-acridinium, which behaves as an intercalating agent, exerts a significant antitumour effect against Ehrlich carcinoma which is amplified by its combination with α-alanine or glycine (Oswald, 1975).

Oncodazole, or *methyl 5-(2-thienylcarbonyl)-1-H-*

benzimidazol-2-yl carbamate, synthetized by Jansen (R17934) exerts an antimitotic effect in vitro (De Brabander et al., 1976) and an antitumoral activity in vivo (Atassi and Tagnon, 1975); it inhibits polymerisation of tubulin (Hoebeke et al., 1976; De Brabander et al., 1976, 1977). Since it is not soluble, intravenous administration of a micronized suspension was attempted, but this caused a poorly predictable toxicity. For this reason the drug is recommended mainly for intrapleural and intraperitoneal administration (Kenis et al., personal communication).

The *retinoid,* ethyl all-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,3,6,8-nomatetraenoate (Ro 10-9359) was shown to exert a strong therapeutic effect on a chemically induced skin papilloma of the mouse after local injection (Matter and Bollag, 1977). The effect of vitamin A and other retinoids on precancerous tissues has also been confirmed in vitro by Lasnitzki (1977), who showed their effect of DNA reduction synthesis. Moreover, vitamin A plasma levels greater than 2 mmol/l may enhance the effect of conventional oncostatics on human cancers (Soukop et al., 1977).

Lycurim or 1,4-di-(methylsulphonyl-oxy-ethyl-amino)-1,4-didesoxy-erythritol-dimethylsulphonate seems also promising for local cytostatic treatment according to Budapest's oncologists (Csetényi et al., 1977).

Local Chemotherapy

Local chemotherapy, for tumours accessible to it, receives more attention: *bleomycin in oil* has given us remarkable regressions of skin breast cancer metastases resistant to systemic chemotherapy and not irradiable because situated in a previously irradiated area (Mathé et al., 1977a); what is most interesting in this result is the fact that breast cancer was not known to be sensitive to bleomycin.

References

Arcamone, F., Benardi, L., Giardino, P., Patelli, B., Di Marco, A., Casazza, A. M., Pratesi, G., Reggiani, P.: Synthesis and antitumour activity of 4-demethoxydaunorubicin, 4-demethoxy-7,9-diepidaunorubicin and their β-anomers. Cancer treat. Rep. **60,** 829–833 (1976)

Astaldi, G.: Peptichemio: a multifaceted antiblastic drug. Wadley med. Bull. **5,** 303–326 (1975)

Atassi, G., Tagnon, H. J.: Comparison of Adriamycin with the DNA-Adriamycin complex in chemotherapy of L1210 leukemia. Europ. J. Cancer **10,** 399–403 (1974)

Atassi, G., Tagnon, H. J.: R 17.934-NSC 238.159: a new antitumour drug. I. Effect on experimental tumors and factors influencing effectiveness. Europ. J. Cancer **11,** 599–607 (1975)

Atassi, G., Duarte-Karim, M., Tagnon, H. J.: Comparison of Adriamycin with DNA-Adriamycin complex in chemotherapy of experimental tumors and metastases. Europ. J. Cancer **11,** 309–316 (1975)

Bachmann, E., Weber, E., Zbinden, G.: Effects of seven anthracyclin antibiotics on electrocardiogram and mitochondrial function of rat hearts. Agent and Actions **5** (4), 383–393 (1975)

Bakowski, M. T.: ICRF 159 (+)1,2-di-(3,5-dioxopiperazin-1-yl)-propane NSC-129,943; Razoxane. Cancer treat. Rev. **3,** 95–107 (1976)

Begg, A. C., Sheldon, P. W., Forster, J. L.: Demonstration of hypoxic cell radiosensitization in solid tumours by metronidazole. Brit. J. Radiol. **47,** 399–404 (1974)

Brandt, L., Könyves, I.: Therapeutic effect of prednimustine (Leo 1031) in various types of leukemia. Europ. J. Cancer **13,** 393–398 (1977)

Brandt, L., Könyves, I., Möller, T. R.: Therapeutic effect of Leo 1031, an alkylating corticosteroid ester, in lymphoproliferative disorders. I. Acta med. scand. **197,** 317–322 (1975)

Brazhnikova, M. G., Konstantinova, N. V.: Antitumor antibiotic nocamycin: isolation and characterization (Abstract 566). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Burchenal, J. H., Kalaher, K., O'Toole, T., Chisholm, J.: Lack of cross-resistance between certain platinum coordination compound in mouse leukaemia. Cancer Res. **37,** 3455–3457 (1977)

Buroker, T., Baker, L., Correa, J., Schwartz, L. A., Vaitkevicius, V. K.: Phase I trial of ftorafur combined with mitomycin C or methyl-CCNU in gastrointestinal cancers. Cancer treat. Rep. **61,** 463–467 (1977)

Calvert, A. H., Price., L. A.: DDMP (2,4-diamino-3′,4′-dichlorophenyl-6-methylpyrimidine) in the treatment of metastatic hypernephroma (Abstract 517). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Casazza, A. M., Di Marco, A., Bertazzoli, C., Formelli, F., Giuliana, G.: Antitumour activity, toxicity and pharmacological properties of 4′-epiadriamycin (Abstract 502). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Cattan, A., Pourny, C., Carpentier, Y., Cattan, E., Barouch, M.: Antimetastasis effect of two derivatives of epipodophyllotoxin in mice. Europ. J. Cancer **12,** 797–805 (1976)

Chauvergne, J., Durand, M.: Essai de chimiothérapie de tumeurs solides par la rubidazone. Bordeaux med. **12,** 1257–1259 (1973)

CMEA studies: Joint clinical study of new antineoplastic agents phase (III). In: Antitumour Drug Therapy Reports **3,** 37–39 (1977)

Colvin, M., Brundrett, R. B., Kan, M. N. N., Jardine, I., Fenselau, C.: Alkylating properties of phosphoramide mustard. Cancer Res. **36,** 1121–1126 (1976)

Connors, T. A., Braddock, P. D., Khokhar, A. R., Tobe, M. L.: New platinum complexes with antitumour activity. Chem. Biol. Interactions **5,** 415–424 (1972)

Connors, T. A., Cumber, A. J., Ross, W. C. J., Clarke, S. A., Mitchley, B. C. V.: Regression of human lung tumor xenografts induced by water-soluble analogs of hexamethylmelamine. Cancer treat. Rep. **61,** 927–928 (1977)

Conroy, P. J., Nodes, J. T., Slater, T. F., White, G. W.: The inhibitory effects of a 4-hydroxy-pentenal: cysteine adduct against sarcoma 180 cells in mice. Europ. J. Cancer **13,** 55–63 (1977)

Csetényi, J., Hegedüs, L., Szamel, I., Bodrogi, I., Kanyar, B., Kerpel-Fronius, S., Eckhardt, S.: Human pharmacokinetic studies of Lycurim (Abstract 612). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

De Barbieri, A., Di Vittorio, P., Perrone, F., Mangeri, M., Agosteo, A. P. Zappa, M., Temelcon, O.: A new class of antitumour glycopeptides (Abstract 521). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

De Brabander, M., Van de Veire, R., Aerts, F., Geuens, G., Desplenter, L., De Cree, J., Borders, M., Janssen, P. A. J.: R 17934: a new synthetic anticancer drug interfering with microtubules. Chemotherapy **8,** 121–127 (1976)

De Brabander, M., Van de Veire, R. M. L., Aerts, F. E. M., Borgers, M. J. M., Janssen, P. A. J.: The effects of methyl (5-(2-thienylcarbonyl)-1H-benzimidazol-2-yl) carbamate (R 17934; NSC 238.159), a new synthetic antitumoral drug interfering with microtubules, on mammalian cells cultured in vitro. Cancer Res. **36,** 905–916 (1976)

De Brabander, M., Geuens, G., Van de Veire, R., Thone, F., Aerts, F., Desplenter, L., De Cree, J., Borgers, M.: The effects of R 17934, a new antimicrotubular substance on the ultrastructure of neoplastic cells in vivo. Europ. J. Cancer **13,** 511–528 (1977)

Depres-De Campeneere, D., Masquelier, M., Trouet, A.: Compared activity of daunorubicin and two derivatives on L1210 leukaemia in vitro and in vivo (Abstract 494). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Di Marco, A., Casazza, A. M., Pratesi, G.: Enhancement by Tween 80 of the antitumour activity of adriamycin on experimental mouse tumours. I.R.S.C. Med. Sci. **4,** 452 (1976)

Di Marco, A., Casazza, A. M., Pratesi, G.: Antitumour activity of 4-demethoxydaunorubicin administered orally. Cancer treat. Rep. **61,** 893–894 (1977)

Dombernowsky, P., Nissen, N. I.: Combination chemotherapy with 4′demethylepipodophyllotoxin-9-(4,6-O-ethylene-β-D-glucopyrasonide), VP 16213 in L1210 leukaemia. Europ. J. Cancer **12,** 181–188 (1976)

Eagan, R. T., Moertel, C. G., Hahn, R. G., Schutt, A. J.: Phase I study of a five day intermittent schedule for 1,2:5,6-dianhydrogalactitol (NSC-132313). J. nat. Cancer Inst. **56,** 179–181 (1976)

Eckhardt, S., Hindy, I., Farkas, E.: Clinical pharmacological studies with formyl-leurosine in malignant diseases, p. 451. In: Proceedings of 9th International Congress of Chemotherapy, London (Eds. K. Hellman and T. A. Connors). New York: Plenum Press 1976

Emanuel, N. M., Konovalova, N. P., Djachkovskaya, R. F.: Antitumour activity of 1,2-bis-diacetyl ethane. Cancer treat. Rep. **60,** 1601–1604 (1976)

EORTC Clinical Screening Group: Epipodophyllotoxin VP 16213 in treatment of acute leukaemias, haematosarcomas and solid tumours. Brit. med. J. **3,** 199–202 (1973)

EORTC Clinical Screening Group: Essai thérapeutique phase II de l'ifosfamide dans les hématosarcomes et les tumeurs solides. Sem. Hôp. Paris **51,** 7–10 (1975)

EORTC Clinical Screening Group: A phase II clinical trial of prednimustine. Biomedicine **27,** 158–161 (1977a)

EORTC Clinical Screening Group: A phase II clinical trial of cytembena. Biomedicine **26,** 392–395 (1977b)

EORTC Clinical Screening Group: A phase II clinical trial of peptichemio. Biomedicine **27,** 290–294 (1977c)

EORTC Cooperative Group for Leukaemias and Haematosarcomas: Clinical screening of epipodophyllotoxin VM 26 in malignant lymphoma and solid tumours. Brit. med. J. **2,** 744–748 (1972)

EORTC Screening and Pharmacology Group: Hexitol derivatives; screening and kinetics. In: Proceedings of a Conference on Galactitol Derivatives, Budapest, September 1977 (in press, 1978)

Farkas, E., Eckhardt, S.: Clinical investigations with formyl-leurosine, p. 457. In: Proceeding of 9th International Congress of Chemotherapy, London (Eds. K. Hellman and T. A. Connors). New York: Plenum Press 1976

Fenelly, J. J.: The role of treosulfan in ovarium carcinoma (Abstract 554). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Fiebig, H. H., Eisenbrand, G., Zeller, W. J., Deutsch-Wenzel, T.: Water soluble derivatives and bifunctional analogs of the anticancer agent 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU). Europ. J. Cancer **13,** 937–945 (1977)

Foster, J. L., Conroy, P. J., Searle, A. J., Willson, R. L.: Metronidazole (flagyl): characterization as a cytotoxic drug specific for hypotoxic tumour cells. Brit. J. Cancer **33,** 485–490 (1976)

Fowler, J. F., Sheldon, P. W., Denekamp, J., Field, S. B.: Optimum fractionation of the C_3H mouse mammary carcinoma using X-rays, the hypoxic-cell radiosensitizer R0-07-0582 or fast neutrons. Int. J. Radiat. Oncol. Biol. Phys. **1,** 579–592 (1976)

Garibjanian, B. T., Jonson, R. K., Kline, I., Vadlamudi, S., Gang, M., Venditti, J. M., Goldin, A.: Comparison of 5-fluorouracil and ftorafur. II. Therapeutic response and development of resistance in murine tumors. Cancer treat. Rep. **60,** 1347–1361 (1976)

Geran, R. I., Congleton, G. F., Dudeck, L. E., Abbott, B. J., Gargus, J. L.: A mouse ependymoblastome as an experimental model for screening potential antineoplastic drugs. Cancer Chemother. Rep. **4** (part 2), 53–87 (1974)

Gershanovich, M. L.: Clinical data on the antitumour activity of hydrazine sulfate. Cancer treat. Rep. **60,** 933–935 (1976)

Gosalves, M., Canero, R. G., Blanco, M.: A screening for selective anticancer agents among plant respiratory inhibitors. Europ. J. Cancer **12,** 1003–1009 (1976)

Hansen, B., Fex, H., Holmberg, K., Högberg, B., Jensen, G., Könyves, I.: Some esters of progestins and alkylating agents and their cytostatic properties (Abstract 506). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Harrap, K. R., Riches, P.G, Gilby, E. D., Sellwood, S. M., Wilkinson, R., Könyves, I.: Studies on the toxicity and antitumour activity of predimustine, a prednisolone ester of chlorambucil. Europ. J. Cancer **13,** 873–881 (1977)

Hayat, M., Mathé, G., Janot, M. M., Potier, P., Dat-Yuong, N., Cavé, A., Sevenet, T., Kan-Fan, C., Poisson, J., Miet, J., Le Men, J., Le Goffic, F., Fouyette, A., Ahond, A., Dalton, L. K., Connors, T. A.: Experimental screening of 3 forms and 19 derivatives or analogs of ellipticine: oncostatic effect on L1210 leukaemia and immunosuppressive effect of 4 of them. Biomedicine **21,** 101–106 (1974)

Hill, B. T., Price, L. A., Harrison, S. I., Goldie, J. H.: Studies on the transport and distribution of diaminopyrimidines in L5178Y lymphoblasts in cell culture. Biochem. Pharmacol. **24,** 535 (1975)

Hill, B. T., Price, L. A., Harrison, S. I., Goldie, J. H.: The difference between "selective folinic acid protection" and "folinic acid rescue" in L5178Y cells culture. Europ. J. Cancer **13,** 861–871 (1977)

Hill, J. M., Loeb, E., Pardue, A. S., Khan, A., Hill, N. O., King, J. J., Hill, R. W.: Platinum coordination compounds in the treatment of acute leukaemia and other malignant diseases with particular reference to malonato 1,2-diaminocyclohexane platinum. J. clin. Hematol. Oncol. **7,** 671–710 (1977)

Hoebeke, J., Van Nijen, G., De Brabander, M.: Interaction of oncodazole (R 17.934), a new antitumoral drug, with rat brain tubulin. Biochem. biophys. Res. Commun. **69,** 319–324 (1976)

Hohorst, H. J., Peter, G., Struck, R. F.: Synthesis of 4-hydroperoxy derivatives of ifosfamide and trofosfamide by direct ozonation and preliminary antitumor evaluation in vivo. Cancer Res. **36,** 2278–2281 (1976)

Husson, H. P., Thevenet, T., Kan, C., Pottier, P.: Alangium vitiense extracts. Phytochemistry (in press, 1977)

Imbach, J. L., Montero, J. L., Moruzzi, A., Serrou, B., Chenu, E., Hayat, M., Mathé, G.: The oncostatic and immunosuppressive actions of new nitrosourea derivatives containing sugar radicals. Biomedicine **23,** 410–413 (1975)

International Holoxan Symposium. 21.–23. 3. 1977, Düsseldorf. Proceedings to be published in 1978

Israel, M., Modest, E. J., Frei, E.: N-trifluoroacetyl adriamycin-14-valerate, an analog with greater experimental antitumour activity and less toxicity than adriamycin. Cancer Res. **35,** 1365–1368 (1975)

Jacquillat, Cl., Weil, M., Gemon-Auclerc, M. F., Izrael, V., Bussel, A., Boiron, M., Bernard, J.: Clinical study of rubidazone (22.050RP) a new daunorubicin-derivated compound, in 170 patients with acute leukemias and other malignancies. Cancer **37,** 653–659 (1976)

Jager, R. de., Brugarolas, A., Hansen, H., Cavalli, F., Wennerholm, A., Kenis, Y., Alberto, P.: Oral dianhydrogalactitol (DAG): phase I–II study. Proc. Amer. Assoc. Clin. Oncol. **18,** 295 (abstract C-114), 1977

Johnson, R. K., Garibjanian, B. T., Houchens, D. P., Kline, I., Gaston, M. R., Syrkin, A. B., Goldin, A.: Comparison of 5-fluorouracil and ftorafur. I. Quantitative and qualitative differences in toxicity to mice. Cancer treat. Rep. **60,** 1335–1345 (1976)

Juret, P., Tanguy, A., Gerard, A., Le Talaer, J. Y., Dat-Xuong, N., Le Pecq, J. B., Paoletti, C.: Therapeutic effect of 9-hydroxy-2-(N)-Methyl-Ellipticine (NSC-264137) in human advanced cancers: preliminary results. Presented at EORTC Early Clinical Trials Meeting, Copenhagen, June 1977. To be published in 1978

Kaufman, J. H., Hanjura, G. L., Mittelman, A., Aungst, C. W., Murphy, G. P.: Study of Leo-1031 (NSC-134087) in lymphocytic lymphoma and chronic lymphocytic leukemia. Cancer Treat. Rep. **60,** 277–279 (1976)

Kohn, K. W., Waring, M. J., Glaubiger, D., Friedman, C. A.: Intercalative binding of ellipticine to DNA. Cancer Res. **35,** 71–76 (1975)

Könyves, I., Nordenskjöld, B., Plym Forshell, G., de Schrijver, A., Westerberg-Larsson, H.: Preliminary clinical and absorption studies with prednimustine in patients with mammary carcinoma. Europ. J. Cancer **11,** 841–844 (1975)

Krishan, A., Israel, M., Modest, J., Frei, E.: Differences in cellular uptake and cytofluorescence of adriamycine and N-trifluoacetyl adriamycin-14-valerate. Cancer Res. **36,** 2108–2110 (1976)

Lasnitzki, I.: Inhibition of precancerous changes by vitamin A and its structural analogues in organ culture (Abstract 588). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Lelieveld, P.: Cell killing effectiveness of hycanthone. Europ. J. Cancer **13,** 897–898 (1977)

Lelieveld, P.: Data reported at EORTC Screening and Pharmacology Group meeting 1977. To be published in 1978

Le Men, J., Hayat, M., Mathé, G., Guillon, J. C., Chenu, E., Humblot, E., Masson, Y.: Methoxy-9-ellipticine lactate. I. Experimental study. Europ. J. clin. biol. Res. **15,** 534–538 (1970)

Lenaz, L., Necco, A., Dasdia, T., Di Marco, A.: Biologic activity of some adriamycin derivatives. Cancer Chemother. Rep. **58,** 769–776 (1974)

Le Pecq, J. B., Dat-Xuong, N., Gosse, C., Paoletti, C.: A new antitumoral agent: 9-hydroxyellipticine. Possibility of a rational design of anticancerous drugs in a series of DNA intercalating drugs. Proc. nat. Acad. Sci. (Wash.) **71,** 5078–5082 (1974)

Le Pecq, J. B., Gosse, C., Dat-Xuong, N., Paoletti, C.: Deux nouveaux dérivés antitumoraux: l'hydroxy-9-methyl-2-ellipticinium (acétate) et l'hydroxy-9-diméthyl-2,6-ellipticinium (chlorure). Action sur la leucémie L1210 de la souris. C.R. Acad. Sci. (Paris) **281,** 1365–1367 (1975)

Le Pecq, J. B., Gosse, C., Dat-Xuong, N., Cros, S., Paoletti, C.: Antitumor activity of 9-hydroxyellipticine (NSC 210717) on L1210 mouse leukemia and the effect of route of injection. Cancer Res. **36,** 3067–3076 (1976)

Levin, V. A., Freeman-Dove, M. A., Maroten, C. E.: Dianhydrogalactitol (NSC-132313): Pharmacokinetics in normal and tumor-bearing rat brain and antitumor activity against three intracerebral rodent tumors. J. nat. Cancer Inst. **56,** 535–539 (1976)

Lutz, D., Böhnel, J., Stacher, A.: Prednimustine treatment in chronic lymphocytic leukaemia (Abstract 505). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Maral, R.: Experimental activities of benzoylhydrazone daunorubicine (rubidazone). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Maral, R., Ducep., J. B., Farge, D., Ponsinet, G., Reisdorf, D.: Preparation et activité antitumorale expérimentale d'un nouvel antibiotique semisynthétique: la diethoxy-14-daunorubicine. C.R. Acad. Sci. (Paris) (in press, 1977)

Mathé, G., Hayat, M., de Vassal, F., Schwarzenberg, L., Schneider, M., Schlumberger, J. R., Jasmin, C., Rosenfeld, C: Methoxy-9-ellipticine lactate. II. Clinical screening. Europ. J. clin. biol. Res. **15,** 541–545 (1970)

Mathé, G., Schwarzenberg, L., Pouillart, P., Oldham, R., Weiner, R., Jasmin, C., Rosenfeld, C., Hayat, M., Misset, J. L., Musset, M., Schneider, M., Amiel, J. L., De Vassal, F.: Two epipodophyllotoxin derivatives VM26 and VP16213, in the treatment of leukemias, hematosarcomas and lymphomas. Cancer **34,** 985–992 (1974)

Mathé, G., Machover, D.: Intra tumour injection of bleomycin (in press, 1977a)

Mathé, G., Hayat, M., Husson, P., Chenu, E.: Oncostatic effects of alangium vitiense extracts, ICIG-EORTC 1131, 1186 and 1207 on lymphoid tumours. Cancer Res. (in press, 1977b)

Mathé, G., Misset, J. L., De Vassal, F., Hayat, M., Machover, D., Belpomme, D., Schwarzenberg, L., Ribaud, P., Musset, M., Jasmin, C.: Phase II clinical trial with vindesine for remission induction in acute leukaemia, blastic crisis of chronic myeloid leukaemia, lymphosarcoma and Hodgkin's disease. Absence of cross-resistance with vincristine. Medical Oncology **3,** S21 (abstract 51) (1977c) and Cancer Treat. Rep. (in press, 1978a)

Mathé, G., Serrou, B., De Vassal, F., Misset, J. L., Schwarzenberg, L., Hayat, M., Machover, D., Ribaud, P., Belpomme, D., Jasmin, C., Musset, M.: Preliminary results of phase I and II clinical trials of RFCNU, a new nitrosourea sugar derivative, in digestive tract tumours. Biomedicine **27,** 294–297 (1977d)

Mathé, G., De Vassal, F., Misset, J. L., Schwarzenberg, L., Hayat, M., Machover, D., Ribaud, P., Belpomme, D., Jasmin, C., Musset, M.: Preliminary results of phase I and II clinical trials of RPCNU a new nitrosourea derivative. Cancer Chemother. Pharmacol. (in press, 1978b)

Mathé, G., Hayat, M., Jasmin, C., Halle-Pannenko, O., Serrou, B., Chenu, E., Bourut, C., Imbach, J. L., Montero, J. L., Moruzzi, A.: Further experimental study of the oncostatic action and side effects of new nitrosourea derivatives. Cancer Chemother. Pharmacol. (in press, 1978c)

Matter, A., Bollag, W.: A fine structural study on the therapeutic effect on an aromatic retinoid on chemically-induced skin papillomas of the mouse. Europ. J. Cancer **13,** 831–838 (1977)

Misset, J. L., Pouillart, P., Belpomme, D., Schwarzenberg, L., Delgado, M., Gil, M., Jasmin, C., Hayat, M., Mathé, G.: Combination chemotherapy with adriamycin, VM26, cyclophosphamide and prednisone in lymphosarcomas and reticulosarcoma. Europ. J. Cancer **13,** 411–414 (1977)

Mittelman, A., Shukla, S. K., Welvaart, K., Murphy, G. P.: Oral estramustine (NSC-89199) in the treatment of advanced (stage

D) carcinoma of the prostate. Cancer Chemother. Rep. **59,** 219–223 (1975)

Mittelman, A., Shukla, S. K., Murphy, G. P.: Extended therapy of stage D carcinoma of the prostate with oral estramustine phosphate. J. Urol. **115,** 409–412 (1976)

Mittelman, A., Catane, R., Murphy, G. P.: New steroidal alkylating agents in advanced stage D carcinoma of the prostate. Cancer treat. Rep. **61,** 307–310 (1977)

Möller, T. R., Brandt, L., Könyves, I., Lindberg, K. G.: Therapeutic effect of Leo 1031, an alkylating corticosteroid ester, in lymphoproliferative disorders, II. Acta med. scand. **197,** 323–327 (1975)

Németh, L., Institoris, L., Somfai, S., Gál, F., Sugár, J., Csuka, O., Szentirmay, Z., Kellner, B.: Pharmacologic and antitumor effect of 1,2:5,6-dianhydrogalactitol (NSC-132313). Cancer Chemother. Rep. **56,** 593–602 (1972)

Newman, H., Vodinelich, L., Potter, C. W.: The effects of 1-β-D-ribofuranosyl-2,2,4-triazole-3-carboxamide (ribavirin) on the transplanted tumours of animal. Europ. J. Cancer **13,** 821–830 (1977)

Nillius, A., Könyves, I.: Oral Estracyt® (estramustine phosphate) in the treatment of advanced carcinoma of the prostate, p. 469. In: Proceedings 9th International Congress Chemotherapy, London (Eds. K. Hellman and T. A. Connors). New York: Plenum Press 1976

Nilsson, T., Jönsson, G.: Clinical results with estramustine phosphate (NSC-89199): a comparison of the intravenous and oral preparations. Cancer Chemother. Rep. **59,** 229–232 (1975)

Oki, T., Matsuzawa, Y., Yashimoto, A., Numata, K., Kitamura, I., Hori, S., Takamatsu, A., Umezawa, H., Ishizuta, M., Naganawa, H., Suda, H., Hamada, M., Takenchi, T.: New antitumor antibiotics aclacinomycins A and B. J. Antibiot. (Tokyo) **28,** 830–840 (1975)

Ossewaarde, T.: Data reported at EORTC Screening and Pharmacology Group meeting, 1977. To be published in 1978

Oswald, H.: Potentiated chemotherapeutic activity of 3,6-diamino-10-methylacridinium by combination with glycine or DL-β-alanine on the Ehrlich carcinoma. Arzneimittel-Forsch. **25,** 1608–1609 (1975)

Pályi, I.: Survival and phase sensitivity of hela cells treated with dianhydrogalactitol (NSC-132313). Cancer Chemother. Rep. **59,** 493–499 (1975)

Panasci, L. C., Green, D. C., Nagourney, R., Fox, P., Schein, P. S.: A structure-activity analysis of chemical and biological parameters of chloro-ethyl nitrosoureas in mice. Cancer Res. **37,** 2615–2618 (1977)

Paoletti, M. C., Cros, S., Sorbara, M. M. R., Gosse, C., Tollon, Y., Moisand, C.: Toxicology. Etudes sur la toxicité de la 9-hydroxyellipticine. C.R. Acad. Sci. (Paris) **278,** 1437–1440 (1974)

Pham-Huu-Chanh, M. M., Sorbara, R., Dat-Xuong, N., Le Pecq, J. B., Paoletti, C.: Pharmacologie. Actions cardio-vasculaires et toxicités de l'hydroxy-9-ellipticine chez le chien. C.R. Acad. Sci. (Paris) **279,** 1039–1042 (1974)

Pouillart, P., Mathé, G., Hoang, Thy, T., Lheritier, J., Poisson, M., Huguenin, P., Gautier, H., Morin, P., Parrot, R.: Treatment of malignant gliomas in adults using a combination of adriamycin, VM26 and CCNU: result of a type II trial. Europ. J. Cancer **13,** 419–424 (1977)

Pratesi, G., Casazza, A. M., Di Marco, A.: Antitumor activity of N-trifluoro-aceto-acetyl adriamycin-14-valerate. Submitted to Cancer treat. Rep. 1978

Price, L. A., Goldie, J. H., Hill, B. T.: Methodichlorophen as an antitumour drug: preliminary report. Brit. med. J. **2,** 20 (1975)

Rodriguez, V., Bodey, G. P., Freireich, E. J., McCredie, K. B., McKelvey, E. M., Tashima, C. K.: Reduction of ifosfamide toxicity using dose fractionation. Cancer Res. **36,** 2945–2948 (1976)

Rozencweig, M., Kenis, Y., Atassi, G., Staquet, M., Duarte-Karim, M.: DNA-Adriamycin complex: preliminary results in animals and man. Cancer Chemother. Rep. **6** (Part 3), 131–136 (1975)

Saphonova, T. S., Cherov, V. A.: Photrin, a new antitumour agent. Antitumor Drug Therapy Reports **3,** 45–46 (1977)

Schein, P.: Nitrosoureas. Paper presented at 10th International Congress Chemotherapy, Zürich, September 1977. To be published in 1978

Seeber, S., Meshkov, T., Schmidt, C. G.: Restoration of adriamycin sensitivity in an adriamycin resistant Ehrlich ascites tumour (Abstract 498). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Somfai-Relle, S., Gati, E., Bencze, J., Gal, F.: New derivatives of dianhydrogalactitol (NSC-132313) with significant antitumor activity (Abstract 614). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Soukop, M., McVie, J. G., Calman, K. C.: Vitamin A status and chemotherapeutic responses in cancer patients (Abstract 590). In: Proceedings 10th International Congress Chemotherapy, Zürich, September 1977

Staquet, M., Rozencweig, M., Duarte-Karim, M., Kenis, Y.: Pharmacokinetics of adriamycin and adriamycin-DNA complex in L1210 mice and men. Europ. J. Cancer **13,** 433–435 (1977)

Syrkin, A. B., Jusktov, S. F., Postolnykov, S. F.: Toxicologic character and some antitumor properties of phytohemagglutinic hanerol. Antitumor Drug Therapy Reports **3,** 47–49 (1977)

Szekerte, M., Driscoll, J. S.: The use of macromolecules as carriers of antitumour drugs. Europ. J. Cancer **13,** 529–537 (1977)

Szumiel, I., Nias, A. H. W.: The effect of combined treatment with a platinum complex and ionising radiation on chinese hamster ovary cells in vitro. Brit. J. Cancer **33,** 450–458 (1976)

Taylor, I. W., Bleehen, N. M.: Changes in sensitivity to radiation and ICRF 159 during the life of monolayer cultures of EMT6 tumour line. Brit. J. Cancer **35,** 587–594 (1977)

Tillian, H. M., Schauenstein, E., Erth, A., Esterbauer, H.: Therapeutic effect if cysteine adducts of α-β-unsaturated aldehydes on Ehrlich ascites tumour of mice. Europ. J. Cancer **12,** 989–993 (1976)

Trouet, A., Deprez-de Campeneere D., de Duve, C.: Chemotherapy through lysosomes with a DNA-Daunorubicin complex. Nature (Lond.) New Biol. **239,** 110 (1972)

Trouet, A., Deprez-de Campeneere, D., de Smedt-Malengreaux M., Atassi, G.: Experimental leukemia chemotherapy with a "lysosomotropic" adriamycin DNA complex. Europ. J. Cancer **10,** 405–411 (1974)

Valdivieso, M., Bodey, G. P., Gottlieb, J. A., Freireich, E. J.: Clinical evaluation of ftorafur (pyrimidine-deoxyribose: N_1-2′-furanidyl-5-fluorouracil. Cancer Res. **36,** 1821–1824 (1976)

Vecchi, A., Cairo, M., Montovani, A., Sironi, M., Spreafico, F.: The comparative antineoplastic activity of adriamycin and N-trifluoroacetyl-adriamycin-14-valerate. Cancer treat. Rep. (in press, 1977)

Wardman, P., Adams, G.: Proceedings of the 8th L.H. Gray Meeting on Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy. Brit. J. Cancer (in press, 1978)

Wiltshaw, E., Carr, B.: Cis-platinum diammine dichloride : clinical experience of the Royal Marsden Hospital and Institute of Cancer Research, London, pp. 178–182. In: Platinum coordination complexes in cancer chemotherapy (Eds. T. A. Connors and J. J. Roberts). Heidelberg, New York, Berlin: Springer Verlag 1974

Zbinden, G.: Inhibition of adriamycin cardiotoxicity by acetyldaunomycin. Experientia (Basel) **31,** 1058–1060 (1975)

Zeller, W. J., Eisenbrand, G., Fiebig, H.: Chemotherapeutic activities of new 2-chloroethylnitrosoureas in rat leukaemia L5222. Comparison of bifunctional and water soluble derivatives of BCNU. J. nat. Cancer Inst. (in press, 1977)

Received December 12, 1977