Cancer Chemother. Pharmacol. 1, 25–34 (1978)

Cancer Chemotherapy and Pharmacology

Short Review

Cardiotoxic Effects of Antitumor Agents

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Summary. *Cardiotoxic effects related to treatment with some antitumor agents (chiefly anthracycline antibiotics, cyclophosphamide, corticosteroids, 5-fluorouracil, and radiation therapy), their association, and contemporaneous administration of other (potentially) cardiotoxic drugs are reviewed.*

Experimental models, clinical findings, and diagnostic methods are briefly described.

Pathogenetic factors and interactions of antitumor drugs with biomembranes, DNA, and immune reactions are discussed.

1. Introduction

Experimental and clinical data indicate that overt or subclinical cardiovascular toxicity can be associated with a variety of drugs (Wenzel, 1967; Herman, 1972; Uslenghi et al., 1975; for an up-to-date review see Deglin et al., 1977). Research on drug-related syndromes has primarily been concerned with myocarditis associated with drug-induced allergic reactions (Bickel, 1960; for a review see Zbinden, 1973) and myocardoses (Wuhrmann, 1972) connected with drugs commonly employed for the treatment of cardiovascular diseases. Evidence has emerged revealing the cardiotoxic properties of other classes of drugs. Among these neuroactive compounds as general anesthetics (Thyrum, 1972), the tricyclic antidepressants, and some antineoplastic agents are most important (Moccetti, 1973; Kuebler et al., 1973; Aviado, 1975; Doerr et al., 1976; Ghione, 1977). The cardiotoxic effect of neuroactive drugs has a high epidemiologic relevance owing to their widespread use and is at least partly accountable for the overlapping activity of these drugs with that of cardioactive compounds through their mutual interaction with catecholaminergic receptors (Aviado, 1975). Observation of the cardiotoxicity of antitumor agents first occurred as an unexpected, delayed fallout of long-term clinical trials, and was later reproduced in experimental animals. This observation was made possible by clinical introduction of drugs and treatment schedules that were able to ensure a protracted survival time to a larger number of tumor patients. Despite the extension of cancer chemotherapy during the last few years, which is still going on, the problem we deal with involves a fairly limited number of patients. Although the emphasis placed upon it may appear unjustified owing to its limited overall prevalence, the study of the cardiotoxic effects of antitumor drugs is gaining momentum because of a desire to learn how to circumvent the limits that this cardiotoxicity places on the application of a unique therapeutic measure to an otherwise untreatable disease. Also to be considered is an interest in observing their mechanism of action as a model for gaining better understanding of the still largely unexplored field of drug and environment-induced cardiopathies.

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2. Experimental Models

This interest in the problem stimulated researchers to look for experimental methods for detecting cardiotoxic activity of antitumor compounds at a preclinical level. The majority of this work was carried out with the anthracyclines, these compounds depress the function of rabbit heart mitochondria (Iwamoto et al., 1974) and the idiorhythmic beating of rat cardiac cell cultures (Seraydarian et al., 1977), neonatal mice cardiac explants (Necco and Dasdia, 1974; Necco et al., 1976), isolated guinea pig atrial preparations (Bossa et al., 1975), and in vitro preparations of whole heart of guinea pig (Kobayashi et al., 1972), rat (Langslet et al., 1974), rabbit (Bertazzoli et al., 1974a and b), or dog (Arena et al., 1972,

0344-5704/78/0001/0025/$ 02.00

1975). The presence of Coenzyme Q_{10} in isolated mitochondria preparation, cardioactive glycosides (ouabain), or the addition of ATP to the solution perfusing the cardiac explants counteract the inhibitory effect.

According to some authors, inotropism is also modified by adriamycin, an antibiotic belonging to the anthracycline group. Its negative inotropic effect upon isolated guinea pig atria is enhanced by lowering the Ca^{2+} concentration of the medium (Bossa et al., 1975), whereas its positive inotropic effect upon isolated guinea pig whole heart preparation is antagonized by the addition of β-blocking agents (Kobayashi et al., 1972). The in vivo experimental models are more suitable for the study of cardiotoxic effect of antitumor drugs and particularly of glycoactive steroids, alkylating agents, and anthracycline antibiotics. Administration of these latter compounds to the intact chick embryo in ovo induces modification of the EKG tracing with myocardiolysis and degeneration of the cardiac ganglia (Pannuti, 1972a and b).

Even if we set aside its technical peculiarities, the embryonated egg model is hardly to be recommended for routine use, particularly because such a closed system gives information of less clinical value than open-end systems like the freely excreting intact laboratory animals. The data gathered from these latter models shall be dealt with separately according to the treatment schedule. The cardiotoxic effects of administration of a single high dose can be quite different from those of a long-term treatment. Intravenous (IV) injection of a very high dose of daunorubicin to the hamster is followed by tachycardia, arrhythmia, EKG modifications, and increase in the catecholamine blood level. Drug-dependent alterations of some structures belonging to the autonomous nervous system may contribute to the origin of these phenomena. In fact their onset is unmodified by the administration of procainamide or lidocaine (or, incidentally, by phenoxybenzamine), but is prevented by the administration of ganglionic blocking agents, reserpine, diphenylhydantoine, quinidine, or β-blocking agents and does not occur in pithed animals (Herman et al., 1969, 1970a and b).

The hamster seems to be the species most susceptibile to the cardiotoxic effect of the administration of a single high dose of anthracyclines, particularly adriamycin (Herman et al., 1971). A small cohort of transient rhythm and EKG alterations is usually observed in other animal species (rat, guinea pig, rabbit, or dog) submitted to an analogous treatment.

Administration of a fairly high single dose of adriamycin to mice is followed by a decrease of nucleic acid precursor incorporation into DNA and RNA of the heart cells (Arena et al., 1972; Rosenoff et al., 1975b; Zedek et al., 1976) and by a sequence of ultrastructural changes effecting the myocardiocytes. The early alterations appearing 10 min after the injection of the drug (10 mg/kg) and localized at the nucleolar level are followed within a few hours by the onset of mitochondrial, cytoplasmic, and fibrillar lesions eventually leading to cell death (Lambertenghi-Deliliers et al., 1975a and b). Much less impressive is the light-microscopic picture (Rosenoff et al., 1975a).

In accordance with these findings is the decrease in the heart index (heart weight to body weight ratio) in juvenile mice (Ghione and Bertazzoli, 1977). In these animals myocardiocyte multiplication goes on after birth (Pelc, 1972; Petersen and Baserga, 1965) for a period of time that depends upon environmental conditions.

Delayed cardiopathic effects are induced in some species of experimental animals by long-term treatment. Adriamycin, for example, induces such effects in the rabbit (Bertazzoli et al., 1974a and b; Olson et al., 1974; Jaenke, 1974), rat (Cargill et al., 1974; Bachmann et al., 1975), and monkey (Denine and Schmidt, 1975). In the rabbit, a congestive heart failure syndrome (analogous to the one observed in humans) is associated with a cumulative dosage greater than 200–400 mg/m^2. The cardiopathy is self-perpetuating even if adriamycin treatment is discontinued after a total dose of 120–160 mg/m^2 has been reached (Jaenke, 1976).

3. Cardiotoxicity of Anthracycline Antibiotics

The data above show that much research related to the cardiopathogenicity of antitumor drugs has been focused on anthracyclines (Buja et al., 1976; Ugoretz, 1976). An exhaustive review has been carried out by Lenaz and Page (1976).

These antibiotics, endowed with a sharp biologic activity (Di Marco, 1975) and high therapeutic efficacy (Carter, 1975), produce a number of undesirable side-effects (e.g., bone marrow depression, mucositis, alopecia, and periphlebitis) whose incidence and intensity can be kept within acceptable limits by employing suitable schedules of treatment (Bonadonna et al., 1975). Spontaneously reversible tachyarrhythmias and nonspecific EKG alterations occur at various dose levels. A more serious problem is represented by congestive heart failure, which usually develops abruptly, with a classic symptomatology. The overall incidence of this type of cardiopathy is very low (1–2%), moreover, its occurrence is scanty and erratic in patients treated with a total dose lower than a certain limit (e.g., with adriamycin less than 500 mg/m^2, (Lefrak et al., 1973; Cortes et al., 1973; Cortes, 1975), but increases markedly at a higher total dose. The onset of the cardiopathic syndrome is frequently delayed.

In the case of daunorubicin long-term treated patients, cardiopathy has an overall incidence of 1.6% and occurs after an interval of 2–280 days (median 60 days, average 80 days) from the last dose administered (Von Hoff et al., 1977). From the time of the first clinical observations (Tan et al., 1967; Mathé et al., 1967; Malpas and Scott, 1969; Marmont et al., 1969; Bonadonna and Monfardini, 1969), the literature has contributed confirmations or details, but has resulted in limited knowledge of the highly relevant clinical problem of finding methods suitable for early detection of threatening cardiopathy in high risk patients. The plasma enzyme assay approach was a total failure. The progressive flattening or inversion of T waves (Gilladoga et al., 1975), or a reduction by 40% or more in the QRS total absolute deflection (Minow et al., 1975c), or a significant increase in the systolic time interval (pre-ejection period to left ventricular ejection time ratio) (Rhinehart et al., 1974) and the QRS-Korotkoff interval (Greco et al., 1975), or the finding of echocardiographic alterations (Ewy et al., 1975) have been considered among the most sensitive noninvasive detectors of impending cardiopathy. Still more experience is needed before their reliability can be fully established. The electron-microscopic examination of bioptic myocardial samples can reveal early drug-induced ultrastructural alterations in rabbits and in humans (Bristow et al., 1976; Billingham et al., 1976), but until now only limited information on the adequacy of this new method in terms of clinical predictability is available.

4. Cardiotoxicity of Other Antitumor Drugs or Agents

Besides the anthracycline derivatives, other cardiopathogenic factors are present among the drugs, agents, or modalities commonly involved in the treatment of tumors. The *ionizing radiations* induce a dose-dependent heart disease (Cohn et al., 1967; Stewart et al., 1967) in humans and in animals (Fajardo and Stewart, 1970), which is characterized by myocardial and endothelial lesions. This action may synergize with the cardiotoxic effect of antitumor drugs, such as adriamycin in experimental animals (Fajardo et al., 1976) and in humans (Gilladoga et al., 1975; Ewy et al., 1976). Radiation-induced tissue injury is enhanced by nearly all of the anticancer drugs (Phillips and Fu, 1976).

Quite different are the features of *cyclophosphamide*-associated cardiotoxicity. Administration of high doses of cyclophosphamide (e.g., 45 mg/kg/day for 4–6 days) can produce the onset of hemorrhagic myocardial necrosis in dogs (O'Connel and Berenbaum, 1974), monkeys (Storb et al., 1970), and humans (Santos et al., 1970; Mulvin and Colvin, 1975). The primary lesions are represented by alterations of the capillary walls with leakage of blood containing high concentrations of cell-toxic metabolite(s). The symptomatology, initially confined to EKG alterations, may lead to rapid and sometimes fatal heart failure.

In some cases cardiotoxic effects may suddenly appear in animals or humans affected by leukemia or lymphoma and treated with regular doses of cyclophosphamide. A quite different mechanism of action may operate in these cases, the cardiotoxic effect being ascribed to the acute hyperkalemia induced by the massive tumor cell necrosis following drug administration (Arsenau et al., 1973; Muggia, 1973). Analogous findings have been described in a leukemic patient treated with prednisone vincristine and daunomycin (Wilson et al., 1977).

The cardiotoxic activity of the *corticosteroids*, another class of compounds widely used in cancer chemotherapy, is ascribed to an electrolyte imbalance characterized by a decrease of the K^+, and/or an increase of Na^+ intracellular levels. Electrolytic steroid cardiopathy with necrosis (Selye, 1961) is worsened by many agents, such as catecholamines (Rona et al., 1961), thyroxine, vasopressine, stress, etc. (Selye and Bajusz, 1959a and b). Furthermore, corticosteroids, even at concentrations slightly higher than physiologic ones, exert (in young rats at least) a selective and strong inhibiting action on the nuclear DNA metabolism of the myocytes (and of the hepatocytes too), while mitochondrial DNA, cellular RNA, and protein synthetic mechanisms are not influenced (Loeb, 1976).

Cardiotoxic effects of still unclear pathogenesis have been observed to be associated with the administration of *steroid* or *diethylstilbestrol estrogenic derivatives* in the treatment of hormone-dependant tumors (Obrecht et al., 1973; Gillette and Blackard 1974; Rossett et al., 1975; Nagel, 1975). Myocardial lesions are induced in experimental animals (rats) by the oral administration of high doses (125 mg/kg for 3 days) of *5-fluorouracil* (Levillain, 1972). This compound accumulates in the myocardium but to a lower extent than in other organs (Liss and Chadwick, 1974).

In humans too, a few cases of clinically relevant cardiotoxic effects with EKG alteration and stenocardia induced by 5-fluorouracil administration have been described (Roth et al., 1975; Stevenson-Lang et al., 1977; Levillain et al., 1974). More or less overt cardiotoxic effects whose occurrence depends in some cases upon the schedule of treatment, are displayed by other compounds endowed with clinical or experimental antitumor activity. Among them are *methotrexate* (Rnsen et al., 1974), *emetine* (Israel et al., 1973), *dehydroemetine* (Israel et al., 1974), and a *podophyllotoxin derivative* (Schechter and Jakson, 1975).

5. Cardiotoxicity of Drug Association

The reason why even sporadic drug-related cardiotoxic events are recorded and subliminal phenomena eagerly looked for is to compile not a desultory anecdotal inventory, but rather an alert list particularly useful for selection of the components of a drug association. As mentioned above, the cardiotoxic effects of two or more agents can add or even create a toxic synergistic effect on the basis of sometimes very complex interactions. As far as adriamycin treatment is concerned, there is evidence that the administration of cyclophosphamide may increase the incidence of cardiopathy (Minow et al., 1975a and b).

Actinomycin D and mithramycin may exacerbate an underlying cardiopathy even when administered more than 1 year after discontinuation of adriamycin treatment (Kushner et al., 1975). This effect is shared by concomitant and even prior radiotherapy in the mediastinal area. Thus doses of adriamycin higher than 400 mg/m^2 should be used in children with cardiac irradiation only if benefits outweigh risks (Prout et al., 1977). The existence of a still poorly understood interaction between nonconcomitant or even widely (10 years) spaced drug and radiation treatments is revealed by the endomyocardial biopsy (Billingham et al., 1976) as well as by the occurrence of recall phenomena i.e., drug-induced reappearance of inflammatory reactions limited to the portal of entry of a previous radiation treatment (D'Angio et al., 1959; Donaldson et al., 1974; Baer and Wilkinson, 1976).

Another peculiar type of interaction eventually leading to appearance of cardiopathic syndromes occurs between mediastinal radiations and corticosteroid therapy. The radiation-induced heart disease kept at bay by the antinflammatory activity of the steroids can suddenly detonate when hormone treatment is discontinued (Castellino et al., 1974).

Particular attention should be devoted to the possibility of occurrence of cardiotoxic phenomena when antitumor drugs are associated with antibacterial antibiotics and/or neuroactive drugs, cardioactive glycosides, or diuretics in a (from other viewpoints) fully justified complex treatment of the severely ill cancer patient. The electrolytic disturbances induced by the administration of high doses of antibiotics, exemplified by carbenicillin-associated hypokalemia (Cabizuca and Desser, 1976) can be aggravated by the diuretic-dependent increased potassium excretion. The examples can be multiplied. The final outcome is the enhancement of the susceptibility of the heart to otherwise subliminal metabolic functional or structural derangements carried out by the rest of the drug cocktail or by endogenous hormonal (Boutet et al., 1976) or exogenous factors.

6. Pathogenesis of Cardiotoxic Effects

The molecular bases of the direct or mediated cardiotoxic activity of antitumor agents are supported by the peculiar mechanism of action that allows these compounds to interfere with the structural metabolism and function of biologically relevant macromolecules. The manifold aspect of these interactions is exemplified by data from research with the anthracyclines. It has been postulated that the cardiotoxicity of adriamycin and daunorubicin is ascribable to the aminosugar moiety allowing the molecule to be taken up by cardiac muscle (Adamson, 1974) or that it is associated with the formation of the aglycone (Wheeler, 1975). The Byfield (1977) hypothesis that not only anthracyclines but all agents and/or schedules of non cycle-dependent drugs may prove to be cardiotoxic to the schedule permitting sufficient access to myocardiocyte DNA does not contradict this. The anthracyclines are bound to DNA (Di Marco, 1975) as well as to intracellular proteins, like spectrin (Mikkelsen, 1977), or to plasma or intracellular membranes (Schwartz, 1976 and 1977), and selectively to some of the components of the latter structures, such as phospholipids (Duarte-Karim et al., 1976). Some characteristics of the macromolecules are altered by binding, as demonstrated by the changes induced in DNA conformation, replication, and transcription, the inhibition of Ca^{2+} transport through a mitochondrial phospholipid solution in a biphasic model system (Bossa et al., 1973) and in mitochondria (Anghileri, 1977), by byphasic modifications of the susceptibility to hypotonic lysis of mammalian erythrocytes treated in vitro with daunorubicin (Schioppacassi et al., 1977), or by the alteration in the surface topology of mammalian erythrocytes treated in vitro with adriamycin (Mikkelsen et al., 1977). The increased hemolysis observed in vivo in leukemic animals treated with daunorubicin is reminiscent of these findings.

According to another interpretation, some substances set free in these animals by drug-conditioned leukemic cell lysis determine a disseminated intravascular coagulation with subsequent mechanical disruption of the erythrocytes forced through the partially obstructed blood vessels (Dietrich et al., 1977). Differential association of anthracycline with cellular membranes may help explain their selective but not exclusive toxicity to some nucleated cells like megakariocytes (Jerushalmy et al., 1977), cardiomyocytes, etc., as well as to non-nucleated constituents of the blood like erythrocytes and platelets. The relevance of the biomembrane function(s) in determining the selectivity of these drugs appears to be even greater when we remember that biomembranes are implicated in the pharmacodynamics of the quinone anticancer agents, which include, among others, anthracycline antibiotics and mitomycin C. The

quinone compounds are activated by the cell microsomal system into a free radical state that is considered to be responsible for the damaging effects on DNA or other macromolecules (Bachur, 1977). Free-radical damage to mebranes is decreased by a seleno-enzyme, glutathione peroxidase. In mice on a selenium-free diet enzyme level decreases and adriamycin cardiotoxicity increases (Locker et al., 1977). The presence of a free-radical scavenger (vitamin E, Myers et al., 1976), or of the unique quinone compound-physiologically present in animal cells, the coenzyme Q_{10} (or ubiquinone) (Ghione and Bertazzoli, 1976; Zbinden et al., 1976), can in some experimental models counteract the cardiotoxic effect of adriamycin without lowering, and possibly enhancing its antitumor efficacy (Bertazzoli and Ghione, 1977). The coenzyme Q system has been exhaustively studied by Folkers et al. (1977) and is used in the treatment of idiopathic myocardiopathies (Yamamura, 1977).

7. Immunity and Cardiotoxicity

The alterations in immune responsivity induced by antitumor drug treatment can play a manifold role in the pathogenesis of cardiopathic epiphenomena.

Some clinical observations in 5-fluorouracil treated subjects (Stevenson-Land et al., 1977), as well as the occurrence of a lag period between the suspension of anthracycline treatment and the sudden onset of cardiac failure, or even the self-perpetuating cardiopathy in adriamycin-intoxicated rabbits (Jaenke, 1976), are consistent with the possibility of a drug-conditioned autoimmune antiheart reaction. Autoimmune phenomena occur in many cardiopathies, not only iatrogenic, but even parasitic or idiopathic (Laufer, 1974; Tan, 1974; Ghione, 1975; Intorp, 1975; Fairfax, 1977). In rabbits chronically intoxicated with adriamycin, the existence of humoral and, more important, cell-mediated antiheart autoimmune reactions is clearly demonstrated (Fioretti et al., 1976; Bajpai and Slanczka, 1977).

The reasons why abnormal immune and/or autoimmune phenomena can occur coincidentally with the administration of antitumor drugs are still unclear. A few mechanisms have been suggested. The drug may modulate the expression of new cellular antigens (Nicolin et al., 1974), set normally confined antigens free through the cell lysis, sensitize the cell to antibodies (Segerling et al., 1975), selectively interfere with the depressor immune system that normally blocks the autoreactive 'forbidden clones' of lymphocytes, or more simply, upset the Ig A machinery and allow the consequential penetration through the mucosae (deprived of their physiologic immune coating) of heterogenetic, mainly bacterial, antigens (Walcher and Isselbacher, 1977) able to elicit an immune response cross reacting with the heart (Kaplan, 1962) or other normal tissues.

The majority of antitumor drugs are known to interfere with the immune system at different levels and with different effects. A compound can depress some functions of the immune system and enhance others. Anthracycline antibiotics, for instance, have been shown to depress some immune reactions (Isetta et al., 1971; Della Bruna and Sanfilippo, 1971) as well as transplantation immunity to normal and tumor tissue allograft (Casazza et al., 1974; Vecchi et al., 1974, 1976; Mantovani et al., 1976), but enhance the primary spleen cell mediated immunity, probably owing to an enrichment in macrophages (Orsini et al., 1977).

At least one of the murine macrophage populations is resistant to the inhibiting activity of adriamycin and less resistant to daunorubicin (Mantovani, 1977). The latter data are consistent with the observations of Casazza et al. (1971), Schwartz and Grindey (1973), and Schwartz and Kanter (1975), on the clear-cut differences in immune interfering activity existing in some experimental models between daunomycin and adriamycin despite the apparently minor differences in their chemical structure.

8. Conclusions

The administration of a variety of drugs, including some of the most active antitumor compounds, can induce cardiopathic effects in humans and in experimental animals. The discussion of problems in this review is intentionally limited to only the antitumor drugs and emphasis is placed chiefly on the anthracycline antibiotics, the compounds that have been most thoroughly studied from this viewpoint (Praga et al., 1975). The administration of anthracycline derivatives can determine early cardiopathic effects, mostly limited to transitory EKG alterations or delayed cumulative dose-dependant severe cardiopathies whose incidence is more than sporadic only when a certain total dose is exceeded. A link between early and delayed cardiotoxic effect can be established by considering the former as the expression of induction phases and the latter as the effect of elicitation of a cell-mediated hypersensitiveness reaction.

Other antitumor agents (e.g., 5-fluorouracil) are associated with the onset of cardiopathic effects. Treatment with high doses of cyclophosphamide can induce primarily vascular lesions leading to onset of hemorrhagic necrotic cardiopathies. Administration of corticosteroids can produce a necrotic cardiomyopathic syndrome. Myocardial and endothelial lesions are caused by mediastinal irradiation. The death of irreplaceable myocardiocytes, and eventually, congestive heart failure are the monotonous outcome of all these events.

Among the factors most prominent in this development, consideration will be focused on the different affinity of various drugs for biomembranes, the formation of highly reactive free radicals, and some phenomena such as electrolyte imbalance, liberation of autoantigens or the free introduction of heterogenetic heartlike unique bacterial antigens, disruption of the omeostatic equilibrium of the cell populations forming the immune system (most probably already upset as a consequence or cause of the tumor) and the occurrence of antibody and cell-mediated autoimmune reactions chiefly directed against the heart. Last but not least, poorly defined genetic and environmental factors shall be considered.

It is hardly necessary to mention that the development of a drug-associated cardiopathy in an immunologically and nutritionally altered cancer patient, in common with every other human or animal illness, is never owing to one sole factor, but always results from a combination of many factors. It is plain, therefore, that both prevention and therapy of antitumor drug-associated cardiopathies cannot rely upon a single remedy, but must be based on a complex strategic approach in a carefully evaluated balance of risk and benefit. Outside the limitation of the total dose, promising results are indicated through the use of different treatment schedules (e.g., giving lower doses of adriamycin weekly instead of higher doses every three weeks) (Weiss et al., 1976), administrations of antidotes (McGuire et al., 1977), a constant survey of factors intrinsic or extrinsic to the myocardium that can influence cardiac function, the use of measures that can counteract nutritional (Ohnuma and Holland, 1977; Locker et al., 1977) and immunologic deficiencies, and lastly, a properly designed intensive treatment for heart failure to be started as soon as the first signs of cardiopathy are detected and protracted for an adequate period of time (Gilladoga et al., 1975).

Research is going on to determine the cardiotoxic effect of other antitumor drugs in an effort to find new compounds or analogs of already known drugs endowed with different pharmacodynamic or pharmacokinetic characteristics and with low or absent cardiotoxicity.

References

Adamson, R. H.: Daunomycin (NSC 82151) and adriamycin (NSC 123127): an hypothesis concerning antitumor activity and toxicity. Cancer Chemother. Rep. Part 1, **58,** 293 (1974)

Anghileri, L. J.: Ca^{2+}-transport inhibition by the antitumor agents adriamycin and daunomycin. Arzneim.-Forsch. **27,** 1177 (1977)

Arena, E., D'Alessandro, N., Dusonchet, L., Gebbia, N., Gerbasi, F., Sanguedolce, R., Rausa, L.: Influence of pharmacokinetic variations on the pharmacologic properties of adriamycin. In: Int. Symposium on Adriamycin. Carter, S. K., Di Marco, A., Ghione, M., Krakoff, I., Mathé, G. (eds.), pp. 96–116. New York: Springer 1972

Arena, E., Arico, M., Biondo, F., D'Alessandro, N., Dusonchet, L., Gebbia, N., Gerbasi, F., Sanguedolce, R., Rausa, L.: Analysis of some probable factors responsible for adriamycin induced cardiotoxicity. Adriamycin Review. Staquet, M., Tagnon, H., Kenis, Y., Bonadonna, G., Carter, S. K., Sokal, G., Trouet, A., Ghione, M., Praga, C., Lenaz, L., Karim, O. S. (eds.), pp. 160–172. Ghent, Belgium: European Press Medikon 1975

Arseneau, J. C., Bagley, C. M., Anderson, T., Canellos, G. P.: Hyperkalaemia, a sequel to chemotherapy of Burkitt's lymphoma. Lancet **1973 I,** 10

Aviado, D. M.: Drug action reaction and interaction II iatrogenic cardiopathies. J. Clin. Pharmacol. **15,** 641 (1975)

Bachmann, E., Weber, E., Zbinden, G.: Effects of seven anthracycline antibiotics on electrocardiogram and mitochondrial function of rat hearts. Agents Actions **514,** 383 (1975)

Bachur, N. R.: A general mechanism for the biological activation of quinone anticancer agents to free radicals. 10th Int. Cong. Chemother. Abstr. 564. Zurich, Sept. 18–23, 1977

Baer, D., Wilkinson, L. S.: Daunomycin, adriamycin and recall effect. Ann. Internal Med. **85** 259 (1976)

Bajpai, P. K., Slanczka, D. J.: Anaphylactic heart failure in adriamycin (NSC 123127) treated rabbits. IRCS Med. Sci. **5,** 363 (1977)

Bertazzoli, C., Ghione, M.: Adriamycin associated cardiotoxicity: research on prevention with coenzyme Q. Pharmacol. Res. Commun. **9,** 235 (1977)

Bertazzoli, C., Dell'Oro, I., Ferni, G., Rovero, C., Solcia, E.: Adriamycin: experimental cardiotoxicity on the rabbit. IRCS Med. Sci. **2,** 1454 (1974a)

Bertazzoli, C., Bellini, O., Caccia, G., Dell'Oro, I., Rovero, C., Sala, L., Solcia, E.: Experimental cardiotoxicity of adriamycin. Abstr. XI. Int. Cancer Congr., Florence, Oct. 1974(b)

Bickel, G.: Allergie et myocarde. Schweiz. Med. Wochenschr. **90,** 912 (1960)

Billingham, M. E., Bristow, M. R., Mason, J. W., Daniels, J. R.: Endomyocardial biopsy evidence of radiation enhancement of adriamycin cardiotoxicity. Circulation **54,** Suppl. 2, 23 (1976)

Bonadonna, G., Monfardini, S.: Cardiac toxicity of daunorubicin. Lancet **1969 I,** 837

Bonadonna, G., Beretta, G., Tancini, G., Brambilla, C., Bajetta, E., de Palo, G. M., de Lena, M., Fossati-Bellani, F., Gasparini, M., Valagussa, P., Veronesi, U.: Adriamycin (NSC-123127) studies at the Istituto Nazionale Tumori, Milan. Cancer Chemother. Rep., Part 3, **6,** 231 (1975)

Bossa, R., Galatulas, I., Tofanetti, O.: Effetto di una serie di farmaci sul trasporto di calcio favorito da un estratto mitocondriale di cellule tumorali. Arch. Ital. Patol. Clin. Tumori **16,** 63 (1973)

Bossa, R., Galatulas, I., Mantovani, E.: Sulla cardiotossicità della Daunomicina e della Adriamicina. G. Ital. Chemioter. **22,** 27 (1975)

Boutet, M., Hüttner, I., Rona, G.: Permeability alteration of sarcolemmal membrane in catecholamine-induced cardiac muscle cell injury. Lab. Invest. **34,** 482 (1976)

Bristow, M. R., Mason, J. W., Billingham, M. E., Daniels, J. R.: Endomyocardial biopsy and systolic time intervals in detection of adriamycin cardiotoxicity. Circulation **54,** Suppl. 2, 80 (1976)

Buja, L. M., Ferrans, V. J., Roberts, W. C.: Myocardial pathology in patients treated with antineoplastic drugs. Circulation **48,** Suppl. 4, 150 (1973)

Byfield, J. E.: Adriamycin cardiac toxicity: a different hypothesis. Cancer Treat. Rep. **61,** 497 (1977)

Cabizuca, S. V., Desser, K. B.: Carbenicillin associated hypokalaemic alkalosis. JAMA **235,** 956 (1976)

Cargill, C., Bachmann, E., Zbinden, G.: Effects of daunomycin and anthramycin on electrocardiogram and mitochondrial metabolism of the rat heart. J. Natl. Cancer Inst. **53,** 481 (1974)

Carter, S. K.: Adriamycin – A review. J. Natl. Cancer Inst. **55,** 1265 (1975)

Casazza, A. M., Di Marco, A., Di Cuonzo, G.: Interference of daunomycin and adriamycin on the growth and regression of murine sarcoma virus (Moloney) tumors in mice. Cancer Res. **31,** 1971 (1971)

Casazza, A. M., Giulioni, F., Isetta, A. M., Soldati, M., di Marco, A.: Immunosuppressive activity of antitumor drug. Comparison between daunomycin and adriamycin. Abstr. 11th Int. Cancer Congr., Florence. Milano: Casa Editrice Ambrosiana, 1974, Vol. 4, p. 754

Castellino, R. A., Glatstein, E., Turbow, M. M., Rosenberg, S., Kaplan, H. S.: Latent radiation injury of lungs or heart activated by steroid withdrawal. Ann. Internal Med. **80,** 593 (1974)

Cohn, K. E., Stewart, J. R., Fajardo, L. F., Hancock, E. W.: Heart disease following radiation. Medicine (Baltimore) **46,** 281 (1967)

Cortes, E. P.: Adriamycin cardiotoxicity – a clinicopathological correlation. Proc. Am. Assoc. Cancer Res. 66th Meet. 171 (1975)

Cortes, E. P., Lutman, G., Wanka, J., Pickren, J., Holland, J. F.: Adriamycin cardiotoxicity in adults with cancer. Clin. Res. **21,** 412 (1973)

D'Angio, G. J., Farber, S., Maddock, C. L.: Potentiation of X-ray effects by actinomycin D. Radiology **73,** 175 (1959)

Deglin, S. M., Deglin, J. M., Chung, E. K.: Drug-induced cardiovascular diseases. Drugs **14,** 29 (1977)

Della Bruna, C., Sanfilippo, A.: Immunosuppressive activity of adriamycin in experimental infection of the mouse with *Nippostrongylus brasiliensis*. Experientia (Basel) **27,** 841 (1971)

Denine, E. P., Schmidt, L. M.: Adriamycin-induced myopathies in the rhesus monkey with emphasis on cardiomyopathy. Proc. Med. Soc. Toxicol., Abstr., p. 81 (1975)

Dietrich, M., Finkl, F., Rasche, H., Pflieger, H., Hoelzer, D.: Verstärkung der intravasolen Haemolyse durch Daunorubicin bei der Rattenleukämie L 5222. Blut **34,** 384 (1977)

Di Marco, A.: Daunomycin (daunorubicin) and adriamycin. Handbook Exp. Pharmacol. **38,** 593 (1975)

Doerr, W., Rossner, J. A., Dittgen, R., Rieger, P., Derks, H., Berg, G.: Cardiomyopathie, idiopathische und erworbene Formen und Ursachen. Berlin-Heidelberg-New York: Springer 1976

Donaldson, S. S., Glick, J. M., Wilber, J. R.: Adriamycin activating a recall phenomenon after radiation therapy. Ann. Internal Med. **81,** 407 (1974)

Duarte-Karim, M., Ruysschaert, J. M., Hildebrand, J.: Affinity of adriamycin to phospholipids. Possible explanation for cardiac mitochondrial lesions. Biochem. Biophys. Res. Commun. **71,** 658 (1976)

Ewy, G. A., Jones, S. E., Groves, B. M., Durie, B. G. M., Wright, I.: Electrocardiographic diagnosis of adriamycin heart disease. Clin. Res. **23,** 115A (1975)

Ewy, G. A., Jones, S., Yauger, H., Groves, B., Gaines, J.: Adriamycin cardiac toxicity potentiation by thoracic radiation. Clin. Res. **24,** 120A (1976)

Fairfax, A. J.: Immunological aspects of chronic heart block – a review. Proc. R. Soc. Med. **70,** 327 (1977)

Fajardo, L. F., Stewart, J. R.: Experimental radiation-induced heart disease. Am. J. Pathol. **59,** 299 (1970)

Fajardo, L. F., Eltringham, J. R., Stewart, J. R.: Combined cardiotoxicity of adriamycin and X radiation. Lab. Invest. **34,** 86 (1976)

Fioretti, A., Ghione, M., Pozzoli, E., Lambertenghi-Deliliers, G.: Autoantibodies and spleen cell mediated cytoxicity in adriamycin induced myocarditis in rabbits. Cancer Res. **36,** 1462 (1976)

Folkers, K., Watanabe, T., Pinphanichakarn, V., Wan, Y. P., Porter, T., Azuma, J., Yamagami, T., Kishi, T., Kishi, H., Iwamoto, Y., Nakamura, R., Williams, R.: Biomedical and Clinical Research on Coenzyme Q in Biomedical and Clinical Aspects of Coenzyme Q. Folkers, K., Yamamura, Y. (eds.), p. 299. Amsterdam: Elsevier Scientific 1977

Ghione, M.: Development of adriamycin (NSC-123127). Cancer Chemother. Rep., Part 3, **6,** 83 (1975)

Ghione, M.: Effetti tossici dei farmaci antitumorali sul sistema cardiovascolare. Rec. Progr. Med. **63,** 382 (1977)

Ghione, M., Bertazzoli, C.: Coenzyme Q and Anthracycline Associated Cardiomyopathy in Biomedical and Clinical Aspects of Coenzyme Q. Folkers, K., Yamamura, Y. (eds.), p. 183. Amsterdam: Elsevier Scientific 1977

Gilladoga, A. C., Manuel, C., Tan, C., Wollner, N., Murphy, M. L.: Cardiotoxicity of adriamycin (NSC-123127) in children. Cancer Chemother. Rep., Part 3, **6,** 209 (1975)

Gillette, R. D., Blackard, C. E.: Risk of cardiovascular complications in patients taking estrogen for prostatic carcinoma. JAMA **229,** 1357 (1974)

Greco, F. A., Merrill, J. M., Brereton, H. D., Rodbard, D.: Noninvasive monitoring of subclinical adriamycin cardiotoxicity by Sphygmo-Recording of the QRS-Korotkoff interval. Clin. Res. **23,** 595A (1975)

Herman, E. H., Schein, P., Farmar, R. M.: Comparative cardiac toxicity of daunomycin in three rodent species. Proc. Soc. Exp. Biol. Med. **130,** 1098–1102 (1969)

Herman, E. H., Schein, P., Farmar, R. M.: Influence of pharmacologic and physiologic pretreatment on acute daunomycin cardiac toxicity in the hamster. Toxicol. appl. Pharmacol. **16,** 335 (1970a)

Herman, E. H., Schein, P., Taylor, O., Waravdekar, V. S.: Effect of various antiarrhythmic drugs on the daunomycin-induced arrhythmia in the hamster. Proc. Soc. Exp. Biol. Med. **133,** 69 (1970b)

Herman, E. H., Mhatre, R., Lee, I. P., Vick, J., Waravdekar, V. S.: A comparison of the cardiovascular actions of daunomycin, adriamycin and N-acetyldaunomycin in hamsters and monkeys. Pharmacologia **6,** 230 (1971)

Herman, F.: Pathologie iatrogéne en cardiologie. Nouv. Presse Med. **6,** 413 (1972)

Intorp, H. W.: Antigene des kardiovaskularen Systems und ihre immunpathologische Bedeutung. München: Urban und Schwarzenberg 1975

Isetta, A. M., Intini, C., Soldati, M.: On the immunodepressive action of adriamycin. Experientia (Basel) **27,** 202 (1971)

Israel, L., Depierre, A., Boutillier, J., Chahinian, P.: Activité anticancerense de l'emetine. Travaux préliminaires. Nouv. Presse Med. **11,** 720 (1973)

Israel, L., Depierre, A., Chahinian, P.: Dehydrohemetin in 50 disseminated carcinomas nonresponsive to other drugs. Proc. Am. Assoc. Cancer Res. **15,** 65th Meet., 11 (1974)

Iwamoto, Y., Hansen, I. L., Porter, T. H.: Inhibition of Co Q_{10} enzymes succinoxidase and MADH oxidase by adriamycin and other quinones having antitumor activity. Biochem. Biophys. Res. Commun. **58,** 633 (1974)

Jaenke, R. S.: An anthracycline antibiotic-induced cardiomyopathy in rabbits. Lab. Invest. **30,** 292 (1974)

Jaenke, R. S.: Delayed and progressive myocardial lesions after adriamycin administration in the rabbit. Cancer Res. **36,** 2958 (1976)

Jerushalmy, Z., Patya, M., Dinkhas, J., Devries, A.: Alteration of rat bone marrow megakaryocytes following administration of cytosine arabinoside, daunomycin and hydroxyurea. Haemostasis **6,** 110 (1977)

Kaplan, M. H., Meyerserian, H. M.: An immunological cross-reaction between group A streptococcal cells and human heart tissue. Lancet **1962 I,** 706

Kobayashi, T., Nakayama, R., Takatani, O., Kimura, K.: Positive chronotropic and inotropic action of new antitumor agent adriamycin and its cardiotoxicity. Jap. J. Circul. **36,** 259 (1972)

Kuebler, W., Kuhn, H., Loogen, F.: Die Kardiomyopathien. Ihre Einteilung nach aetiologischen und klinischen Gesichtspunkten. Z. Kardiol. **62,** 3 (1973)

Kushner, J. P., Hansen, V. L., Hammar, S. P.: Cardiomyopathy after widely separated courses of adriamycin exacerbated by actinomycin D and mithramycin. Cancer **36,** 1577 (1975)

Lambertenghi-Deliliers, G., Bellini, O., Franceschini, F., Sala, L.: Alterazioni ultrastrutturali del miocardio indotte da adriamicina. Com., 1° Riun. Sci. Assoc. Ital. Oncol. Med., Napoli maggio 1975a

Lambertenghi-Deliliers, G., Pozzoli, G., Praga, C., Polli, E.: The pathogenesis of adriamycin cardiomyopathy: an ultrastructural study. Abstr. 3rd Meet. Eur-African Division Int. Soc. Haematol. London, Aug. 1975b

Langslet, A., Øye, I., Lie, S. O.: Decreased cardiac toxicity of adriamycin and daunorubicin when bound to DNA. Acta Pharmacol. Toxicol. **35,** 379 (1974)

Laufer, A.: Human and experimental myocarditis, the possible role of immune process in pathogenesis. Isr. Med. J. **27,** 37 (1975)

Lefrak, E. A., Pitha, J., Rosenheim, S., Gottlieb, J. A.: A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer **32,** 302 (1973)

Lenaz, L., Page, J. A.: Cardiotoxicity of adriamycin and related anthracyclines. Cancer Treat. Rev. **3,** 111 (1976)

Levillain, R.: Myocardite experimentale: étude anatomique de 210 coeurs de rats ayant ingeré du 5-fluorouracile. C.R. Acad. Sci. [D] (Paris) **166,** 340 (1972)

Levillain, R., Ramona, F., Cluzan, R.: Utilité eventuelle des examens cardiaques repetés chez le cancereux subissant une chimothérapie intensive et prolongée (Reflexions suggerées par des constatations éxperimentales chez le rat). Ther. **29,** 101 (1974)

Liss, R. N., Chadwich, M.: Correlation of 5-fluorouracil (NSC-19893) distribution in rodents with toxicity and chemotherapy in man. Cancer Chemother. Rep. **58,** 777 (1974)

Locker, G. Y., Doroshow, J. H., Myers, C. E.: Glutathione peroxidase: its role in adriamycin cardiotoxicity. Abstr. 348 Am. Assoc. Cancer Res., 68th Meet., Denver (Colorado), May 18–21, 1977

Loeb, J. N.: Corticosteroids and growth. N. Engl. J. Med. **295,** 547 (1976)

Malpas, J. S., Scott, R. B.: Daunorubicin in acute myelocytic leukemia. Lancet **1969 I,** 469

Mantovani, A.: In vitro and in vivo cytotoxicity of adriamycin and daunomycin for murine macrophages. Cancer Res. **37,** 815 (1977)

Mantovani, A., Vecchi, A., Tagliabue, A., Spreafico, F.: The effects of adriamycin and daunomycin on cellular and hormonal effector mechanism in allogeneic tumor model. Eur. J. Cancer **12,** 371 (1976)

Mantovani, A., Tagliabue, A., Vecchi, A., Spreafico, F.: Effects of adriamycin and daunomycin on spleen cell populations in normal and tumor allografted mice. Eur. J. Cancer **12,** 381 (1976)

Marmont, A. M., Damasio, E., Rossi, F.: Cardiac toxicity of Daunorubicin. Lancet **1969 I,** 837

Mathé, G., Schwarzenberg, L., Schneider, M., Schlumberger, J. R., Hayat, M., Amiel, J. L., Cattan, A., Jasmin, C.: Acute lymphoblastic leukemia treated with a combination of prednison, vincristine and rubidomycin. Lancet **1967 II,** 380

McGuire, W., Young, R. C., Grotzinger, K., Myers, C. E.: Effects of tocopherol and adriamycin-induced cardiomyopathy and tumor response. Abstr. 339, Am. Assoc. Cancer Res., 68th Meet., Denver (Colorado), May 18–21, 1977

Minow, R. A., Benjamin, R. S., Gottlieb, J. A.: Adriamycin (NSC-123127) cardiomyopathy. An overview with determination of risk factors. Cancer Chemother. Rep., Part 3, 195 (1975a)

Minow, R. A., Benjamin, R. S., Gottlieb, J. A.: Concurrent cyclophosphamide, mediastinal radiotherapy and other factors increasing the risk of adriamycin-induced cardiomyopathy. Clin. Res. **23,** 341A (1975b)

Minow, R. A., Gottlieb, J. A., Freireich, E. J.: Electrocardiogram QRS voltage changes in adriamycin cardiomyopathy. Proc. Am. Assoc. Cancer Res., 66th Meet. **87,** Abstr. 345 (1975c)

Mikkelsen, R. B., Lin, P. S., Wallach, D. F. H.: Interaction of adriamycin with human red blood cells: a biochemical and morphological study. J. Mol. Med. **2,** 33 (1977)

Moccetti, T.: Kardiotoxische Medikamente. Schweiz. Med. Wochenschr. **103,** 621 (1973)

Muggia, F. M.: Hyperkalaemia and chemotherapy. Lancet **1973 I,** 602

Mulvin, G. M., Colvin, M.: Intensive cyclophosphamide (NSC-26271) therapy for solid tumors. Cancer Chemother. Rep. Part 1, **59,** 411 (1975)

Myers, C. E., McGuire, W., Young, R.: Adriamycin: amelioration of toxicity by alpha-tocopherol. Cancer Treat. Rep. **60,** 961 (1976)

Nagel, R.: Der heutige Stand der Diagnostik und Therapie des Prostatakarzinoms. Praxis **64,** 1529 (1975)

Necco, A., Dasdia, T.: Daunomycin and adriamycin – effects on the beating rate and rhythm of single cardiac cells grown in vitro. IRCS Med. Sci. **2,** 1293 (1974)

Necco, A., Dasdia, T., Di Francesco, D., Ferroni, A.: Action of ouabain, oligomycin and glucagon on cultured heart cells treated with adriamycin. Pharmacol. Res. Commun. **8,** 105 (1976)

Nicolin, A., Bini, A., Coronetti, E.: Cellular immune response to a drug treated L5178Y lymphoma subline. Nature (Lond.) **251,** 654 (1974)

Obrecht, J. P., Mayr, A. C., Nagel, G.: Die internistische Behandlung des Prostata-, Corpus uteri- und Nierenkarzinoms (Hypernephrom). Schweiz. Med. Wochenschr. **103,** 1414 (1973)

O'Connel, T. X., Berenbaum, M. D.: Cardiac and pulmonary effects of high doses of cyclophosphamide and isophosphamide. Cancer Res. **34,** 1586 (1974)

Ohnuma, T., Holland, J. F.: Nutritional consequences of cancer chemotherapy and immunotherapy. Cancer Res. **37,** 2395 (1977)

Olsen, E. G. J.: Structural and ultrastructural basis of myocardial disease. Proc. R. Soc. Med. **69,** 195 (1976)

Olson, H. M., Young, D. M., Prieur, D. J., Leroy, A. F., Reagan, R. L.: Electrolyte and morphologic alterations of myocardium in adriamycin treated rabbits. Am. J. Pathol. **77,** 439 (1974)

Orsini, F., Pavelic, Z., Mihic, E.: Increased primary cell-mediated immunity in culture subsequent to adriamycin or daunorubicin treatment of spleen donor mice. Cancer Res. **37,** 1719 (1977)

Pannuti, F.: Valutazione preclinica della cardiotossicità di alcune antracicline ad attività antiblastica mediante il "test dell'uovo" studio microelettrocardiografico (MECG). Nota I – la daunomicina. Riv. Patol. Clin. **27,** 1 (1972a)

Pannuti, F.: Valutazione preclinica della cardiotossicità di alcune antracicline ad attività antiblastica mediante il "test dell'uovo" studio microelettrocardiografico (MECG). Nota II – l'adriamicina. Riv. Patol. Clin. **27,** 49 (1972b)

Pelc, S. R.: Influence of metabolic DNA on determinations of the cell cycle. Int. Rev. Cytol. **32,** 327 (1972)

Petersen, R. O., Baserga, R.: Nucleid acid and protein synthesis in cardiac muscle of growing and adult mice. Exp. Cell Res. **40,** 340 (1965)

Phillips, T. L., Fu, K. K.: Quantification of combined radiation therapy and chemotherapy effects on critical normal tissue. Cancer **32,** Suppl. 2, 1186 (1976)

Praga, C., Foa, P., Necco, A. M., Bertazzoli, C.: Adriamycin and daunorubicin cardiotoxicity. In: Adriamycin – Review. Staquet, M., Tagnon, H., Kenis, Y., Bonadonna, G., Carter, S. K., Sokal, G., Trouet, A., Ghione, M., Praga, C., Lenaz, L., Karim, O. S. (eds.), Part II, p. 132. Ghent, Belgium: European Press Medikon 1975

Prout, M. N., Richards, M. J. S., Chung, K. J., Joo, P., Davis, H. L., Jr.: Adriamycin cardiotoxicity in children. Case reports, literature, review and risk factors. Cancer **39,** 62 (1977)

Rinehart, J. J., Lewis, R. P., Belcerzeck, S. O.: Adriamycin cardiotoxicity in man. Ann. Internal Med. **81,** 475 (1974)

Rona, G., Chappel, C. I., Gaudry, R.: Effect of dietary sodium and potassium content on myocardial necrosis elicited by isoproterenol. Lab. Invest. **10,** 892 (1961)

Rosen, G., Suwansirikul, S., Kwon, C., Tan, C., Wu, S. J., Beattie, E. J., Jr., Murphy, M. L.: High-dose methotrexate with citrovarum factor rescue and adriamycin in childhood osteogenic sarcoma. Cancer **33,** 1151 (1974)

Rosenoff, S. H., Brooks, E., Bostick, F., Young, R. C.: Alterations in DNA synthesis in cardiac tissue induced by adriamycin in vivo – Relationship to fatal toxicity. Biochem. Pharmacol. **24,** 1098 (1975a)

Rosenoff, S. H., Olson, H. M., Young, D. M., Bostick, F., Young, R. C.: Adriamycin-induced cardiac damage in the mouse: a small animal model of cardiotoxicity. J. Natl. Cancer Inst. **55,** 191 (1975b)

Rosset, G., Barrelet, L., Alberto, P.: Traitment palliatif du cancer du sein metastatique par le diphosphatase de diethyldioxystilbene. Schweiz. Med. Wochenschr. **105,** 1388 (1975)

Roth, A., Kolaric, K., Popovic, S.: Cardiotoxicity of 5-fluorouracil (NSC-19893). Cancer Chemother. Rep. Part 1, **59,** 1051 (1975)

Santos, G. W., Sensenbrenner, L. L., Burke, P. J., Colvin, O. M., Owens, A. H., Bias, W., Slavin, R.: Marrow transplants in man utilizing cyclophosphamide: Summary of Baltimore experience. Exp. Hematol. **20,** 78 (1970)

Schechter, J. P., Jakson, R. A.: Myocardial infarction in a 27-year-old woman: possible complication of treatment with VP-16-213 (NSC-141540) mediastinal irradiation or both. Cancer Chemother. Rep. Part 1, **59,** 887 (1975)

Schioppacassi, G., Kanter, P. M., Schwartz, H. S.: Membrane actions of daunorubicin in mammalian erythrocytes. 10th Int. Congr. Chemother., Abstr. 497, Zürich, Sept. 12–23, 1977

Schwartz, H. S.: Mechanism and selectivity of anthracycline aminoglycosides and other intercalating agents. Biomedicine **24,** 317 (1976)

Schwartz, H. S.: Mechanism of selective toxicity of intercalating agents. 10th Int. Congr. Chemother. Symposium 101, Zürich, Sept. 18–23, 1977

Schwartz, H. S., Grindey, G. B.: Adriamycin and daunorubicin a comparison of antitumor activities and tissue uptake in mice following immunosuppression. Cancer. Res. **33,** 1837 (1973)

Schwartz, H. S., Kanter, P. M.: Cell interactions: determinant of selective toxicity of adriamycin (NSC-123127) and daunorubicin (NSC-82151). Cancer Chemother. Rep. **6,** 107 (1975)

Segerling, M., Ohanian, S. M., Borsos, T.: Chemotherapeutic drugs increase killing of tumor cells by antibody and complement. Science **188,** 55 (1975)

Selye, H., Bajusz, E.: Sensitization by potassium deficiency for the production of myocardial necrosis by stress. Am. J. Pathol. **35,** 525 (1959a)

Selye, H., Bajusz, E.: Conditioning by corticoids for the production of cardiac lesions with noradrenaline. Acta Endocrinol. **30,** 183 (1959b)

Selye, H.: The pluricausal cardiopathies. Springfield Ill.: Thomas 1961

Seraydarian, M. W., Artaza, L., Goodman, M. F.: Adriamycin: effect on mammalian cardiac cells in culture. 1. Cell population and energy metabolism. J. Mol. Cell. Cardiol. **9,** 375 (1977)

Stevenson-Lang, D., Mikhailidis, P., Gillett, D. S.: Cardiotoxicity of 5-fluorouracil. Lancet **1977 II,** 406

Stewart, J. R., Cohn, K. E., Fajardo, L. F., Hancock, E. W., Kaplan, H. S.: Radiation induced heart disease. A study of twenty-five patients. Radiology **89,** 302 (1967)

Storb, R. C., Buckner, D., Dillingham, L. A., Thomas, E. D.: Cyclophosphamide regimens in rhesus monkeys with and without marrow infusions. Cancer Res. **34,** 2195 (1970)

Tan, C., Tasaka, H., Yu, K. P., Murphy, M. L., Karnofsky, D. A.: Daunomycin an antitumor antibiotic in the treatment of neoplastic disease. Cancer **20,** 333 (1967)

Tan, E. M.: Drug induced autoimmune disease. Fed. Proc. **33,** 1894 (1974)

Thyrum P. T.: Fluorinated hydrocarbons and the heart. Anesthesiology **36,** 103 (1972)

Ugoretz, R. J.: Cardiac effects of doxorubicin therapy of neoplasms. JAMA **236,** 295 (1976)

Uslenghi, E., Russo, P., Dessy, P.: Patologia iatrogenica in ambito cardiovascolare. Minerva Med. **66,** 2841 (1975)

Vecchi, A., Mantovani, A., Barale, C., Spreafico, F.: Differential activity on humoral and cell mediated immunity of adriamycin and daunomycin. Abstr. 11th Int. Cancer Congr. Florence: Casa Editrice Ambrosiana 1974, Vol. 3, p. 381

Vecchi, A., Mantovani, A., Tagliabue, A., Spreafico, F.: A characterization of the immunosuppressive activity of adriamycin and daunomycin on humoral antibody production and tumor allograft rejection. Cancer Res. **36,** 1222 (1976)

Von Hoff, D. D., Rosencweig, M., Layard, M., Slavik, M., Muggia, F. M.: Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. Am. J. Med. **62,** 200 (1977)

Vorbeck, M. L., Malawski, E. F., Erhart, L. S., Martin, A. P.: Membrane phospholipid metabolism in the isoproterenol-induced caromyopathy of the rat. In: Recent Advances in Studies on Cardiac Structure and Metabolism, Vol. 6. Pathophysiology and Morphology of Myocardial Cell Alteration. Fleckenstein, A., Rona, G. (eds.), p. 175. Baltimore: University Park Press 1975

Walcher, W. A., Isselbacher, K. J.: Intestinal antibodies. N. Engl. J. Med. **297,** 767 (1977)

Weiss, A. J., Metter, G. E., Fletcher, W. S.: The cardiac toxicity of adriamycin. Proc. Am. Assoc. Cancer Res., 67th Meet., p. 177, 1976

Wenzel, D. G.: Drug-induced cardiomyopathies. J. Pharm. Sci. **56,** 1209 (1967)

Wheeler, D. M. S.: Another hypothesis concerning the antitumor activity and cardiotoxicity of daunorubicin (NSC-82151) and adriamycin (NSC-123127). Cancer Chemother. Rep. Part 1, **59,** 258 (1975)

Wilson, D., Stewart, A., Szwed, J., Einhorn, L. H.: Cardiac arrest due to hyperkalemia following therapy for acute lymphoblastic leukemia. Cancer **39,** 2290 (1977)

Wuhrmann, F.: Myokardosen im Rahmen der Kardiomyopathien. Schweiz. Med. Wochenschr. **102,** 291 (1972)

Yamamura, Y.: Clinical status of Coenzyme Q and prospects. In: Biomedical and Clinical Aspects of Coenzyme Q. Folkers, K., Yamamura, Y. (eds.), p. 281. Amsterdam: Elsevier Scientific 1977

Zbinden, G.: Progress in toxicology – Special topics – Vol. 1, p. 52. New York: Springer 1973

Zbinden, G., Bachmann, E., Bollinger, H.: Study of coenzyme Q in toxicity of adriamycin in Biomedical and Clinical Aspects of Coenzyme Q. Folkers, K. Yamamura, Y. (eds.). Amsterdam: Elsevier Scientific 1977

Zedeck, M. S., Formelli, F., Sternberg, S. S., Philips, F. S.: Effect of adriamycin in mouse heart. Abstr. 65. A.A.C.R. 67th Meet., Toronto, Canada, May 4–8, 1976

Received November 21, 1977