Success and Failure in Present Chemotherapy and the Implications of Asparaginase

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Success and failure in chemotherapy mean many things to many people, and so in discussing this subject there must first be a definition of terms. Success might be merely making the patient feel better without any objective evidence of improvement. From the patient's point of view, this would constitute at least limited success. Naturally such subjective criteria are hard to evaluate, and the beneficial effects of placebos given in combination with tender loving care are well known. On the other hand, subjective improvement, as evaluated by the performance status of Karnofsky and Burchenal (37), can demonstrate useful and real improvement.

A second criterion of success is objective improvement, such as a 50% shrinkage of a visible or palpable lesion, even though not necessarily accompanied by any great improvement in the patient's condition. In some situations where a tumor is rapidly growing, even a cessation of tumor growth without any regression, if maintained for a long period of time without significant toxicity, would be of value. Objective criteria are frequently limited to those tumors that can be seen, palpated, or demonstrated by X-ray. It is only with a few tumors that we have precise technics for measuring tumor growth, and it is perhaps not surprising that some of these tumors are the ones which have responded best to chemotherapy. We desperately need precise measurements of antitumor effects in other solid tumors in order to determine whether chemotherapy is having some effect and should therefore be continued, or whether it is without effect and should be abandoned.

The six forms of neoplastic disease, uterine choriocarcinoma, Wilms' tumor, testicular tumors, Burkitt's tumor, Hodgkin's disease, and leukemia, which I have selected for discussion, are all amenable to varying degrees of precision in measuring tumor growth. In choriocarcinoma, the presence of trophoblastic cells can be determined very accurately with assays of the urinary chorionic gonadotrophin. With Wilms' tumor, by far the best results have occurred in the pulmonary form of the disease in which the lesions can be watched closely with a radiograph. Testicular tumors most frequently metastasize to the lungs, and these lesions, as well as the Wilms' tumor, can be followed radiographically. In Burkitt's tumor, many of the tumors occur in the jaw and can be easily measured. In Stages III and IV of Hodgkin's disease, fever is frequently a sign of activity of the disease, and defervescence is a sign of early therapeutic effect. In the leukemias, the peripheral blood and the bone marrow provide excellent indices of therapeutic effect. It has been calculated, however, that the average patient with acute leukemia in relapse probably has $10^{12}$ leukemic cells (27). Thus, it should be borne in mind that a decrease in the number of leukemic cells of 2 to 4 logs might be sufficient to produce a normal-appearing marrow, but, that even with a normal number of blast cells in the marrow, the patient might still have a leukemic cell burden of $10^8$ to $10^{10}$ cells. Mathé et al. (50) have advocated a greater degree of precision in evaluating complete remissions by examining marrow aspirations from six different sites, as well as biopsies from the liver, kidney, and testis.

Complete remissions are usually equated with success, but we should also consider the dimension of time in what we mean by success or failure. In the parlance of the space age, we might liken remissions to two kinds of rockets, e.g., one that goes up and then falls back to earth and the other that goes up and remains in orbit. In choriocarcinoma, does success mean the first fall of the chorionic gonadotrophin and disappearance of visualizable metastases, or does it mean a complete cure without maintenance for over 5 years? In acute leukemia, does it mean the initiation of a complete but temporary remission, or does it mean a 5-year survival without evidence of disease?

In choriocarcinoma of the female, up to 95% will show some chemotherapeutic effect, as evidenced by a fall in the urinary chorionic gonadotrophin and a decrease in size of metastatic nodules in the lungs on X-ray examination (33, 44) (Table 1). After continued courses of therapy, approximately 50% of these will be brought into long-term remissions with Methotrexate. Fifty percent of the remainder will be brought into long-term remissions with actinomycin D and will not relapse when taken off therapy. Figures from the earliest series (1955–1956), compiled by J. Lewis, Jr. (42), show that 160 out of 279 or 57% went into complete remission and remained in remission without further therapy. More recent studies show approximately 75% long-term remission (42, 60). In choriocarcinoma, the treatments of choice are Methotrexate (33, 34, 42, 44) and actinomycin D (42, 43, 60) although other agents such as 6-mercaptopurine (2, 3, 61), vinblastine (35), and diazo-oxo-L-norleucine (38) have also shown...
Present Chemotherapy and Asparaginase

Table 1

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
<th>Initial</th>
<th>Long-term</th>
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<tr>
<td>Choriocarcinoma 1955–1966 (42)</td>
<td>279</td>
<td>95%</td>
<td>57%</td>
</tr>
<tr>
<td>Choriocarcinoma 1965–1966 (42)</td>
<td>58</td>
<td>95%</td>
<td>75%</td>
</tr>
<tr>
<td>Wilms' Farber A (25)</td>
<td>31</td>
<td>58% (2–9 yr.)</td>
<td>56% (2+ yr.)</td>
</tr>
<tr>
<td>Wilms' Farber B (25)</td>
<td>55</td>
<td>24% (2+ yr.)</td>
<td>35% (6–12 yr.)</td>
</tr>
<tr>
<td>Wilms' Tan 1956–1964 (personal communication)</td>
<td>23</td>
<td>57% (2–9 yr.)</td>
<td>24% (2+ yr.)</td>
</tr>
<tr>
<td>Testicular tumors (43, 45, 46, 48)</td>
<td>154</td>
<td>15%</td>
<td>8% (1–10 yr.)</td>
</tr>
<tr>
<td>Burkitt's tumor (8, 16, 20, 55)</td>
<td>245</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Burkitt's tumor Ziegler (personal communication) Stage I + II</td>
<td>12</td>
<td>100%</td>
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</tr>
<tr>
<td>Burkitt's tumor Ziegler (personal communication) Stage III</td>
<td>38</td>
<td>74%</td>
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<tr>
<td>Burkitt's tumor Ziegler (personal communication) Stage IV</td>
<td>7</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Burkitt's tumor (U. S.) Carbone (18)</td>
<td>12</td>
<td>50% (1–2 yr.)</td>
<td></td>
</tr>
<tr>
<td>Hodgkin's disease DeVita Stage III + IV (21)</td>
<td>43</td>
<td>81%</td>
<td>&gt;2 yr.</td>
</tr>
</tbody>
</table>

Incidence of initial and long-term remissions.

a. Of those patients surviving 30 days of therapy.

b. There were almost no patient relapses with choriocarcinoma or Burkitt's tumor in unmaintained remission for over 1 year.

c. Eighteen of 35 patients (51%) still in remission at time of report.

Beneficial effects. I. H. Krakoff (personal communication) has treated three patients resistant to Methotrexate and actinomycin D with L-asparaginase (A-ase). There has been a fall in chorionic gonadotropin in all these cases but no evidence of concomitant clinical benefits.

In testicular tumors, investigators at Memorial Hospital (43, 45, 46, 48) reported 24 complete remissions out of 154 patients given chemotherapy. Most of these patients were treated with actinomycin D alone or in combination with Chlorambucil and Methotrexate. Of these 24 complete remissions, 13 or 8% of the total were alive and well with no evidence of disease 11 to 85 months after the beginning of chemotherapy (Table 1). The effects of such combination therapy (46) on the urinary chorionic gonadotropin titer are shown in Chart 1. Fig. 1 shows the effects of therapy on pulmonary metastases in a young male with choriocarcinoma of the testis, and Fig. 2 shows the effects of therapy on pulmonary metastases from embryonal carcinoma of the testis. Both patients are now living and well and have no evidence of disease after more than 10 years of unmaintained remission.

In Wilms' tumor, the pulmonary metastases are most suitable for precise measurements, and the pulmonary form of Wilms' tumor has been by far the most amenable to therapy. Farber (25) reported that 18 out of 31 patients or 58% with metastatic Wilms' tumor first seen at the Children's Hospital in Boston had long remissions following radiation therapy and actinomycin D and were without evidence of disease for from 2 to 9 years following the diagnosis. C. T. C. Tan (personal communication) has reported that, in a series of patients with pulmonary metastases at Memorial Hospital initially treated elsewhere, 8 out of 23 patients have had long-term remissions (6 to 10 years) following actinomycin D with or without radiotherapy (Table 1).

Burkitt's tumor (15) in Africa treated by Burkitt (16), Ngu (55), or Clifford (20) with either large doses of Cytoxan (40 mg/kg) or Orthomerphalan (1.2 mg/kg) intravenously showed originally about 15% long-term remissions, and 38 out of their 245 patients so treated remained in remission for over a year without maintenance therapy (8) (Table 1). Since patients with this disease rarely relapse if they remain in remission for over a year, these remissions can be considered somewhat similar to 5-year cures. More recent studies by Morrow et al. (51) have shown that approximately 20% of the total and 80% of the Stage I patients at Kampala have gone into long-term remission.

Chart 1. Effects of combination therapy on urinary chorionic gonadotropin levels of patient with choriocarcinoma of the testis (46).
remissions. Recent studies by J. Ziegler (personal communication) of the Lymphoma Treatment Center in Kampala have shown that, with the initial Cytoxan therapy of 40 mg/kg either as a single dose or repeated every 2 to 3 weeks for 6 doses, complete remissions developed in 42 of 57 consecutive, previously untreated patients with Burkitt’s tumor (Table 1). Complete remissions were achieved in 12 out of 12 patients with Stage I or II disease. At last report, 38 of 42 were still in complete remissions, but it is too early to say how many will go on to long-term remissions. It is of interest, however, that Carbone et al. (18), reporting on 12 patients with American Burkitt’s tumor treated with this multiple-dose Cytoxan therapy, showed 6 of the 12 with no evidence of disease for periods of 50 to 112 weeks.

The recent report of DeVita et al. (21) on the combination treatment of Stages III and IV of Hodgkin’s disease is very exciting (Table 1). Forty-three patients were given six 2-week cycles of therapy consisting of vincristine (1.4 mg/sq m) and nitrogen mustard (6 mg/sq m) on Days 1 and 8, procarbazine (100 mg/sq m) daily for 14 days of each cycle, and prednisone (40 mg/sq m) p.o. for 14 days of Cycles 1 and 4. At the end of the 6 cycles, no further therapy was given. Remissions were achieved in 35 out of 43 patients; 18 of these were still in remission and 12 for more than 24 months after discontinuation of therapy (Table 1).

If the differences in the incidence of long-term remissions between Stages I and II of Burkitt’s tumor can be extrapolated to Hodgkin’s disease, one would expect even better results in early localized cases than these relatively excellent results achieved in the advanced disease. This treatment regimen is presently being studied in all stages of Hodgkin’s disease by Ziegler et al. (personal communication) at the Lymphoma Treatment Center in Uganda where radiotherapy is not available. The results in Stages I and II of the disease will be eagerly awaited by all those investigators interested in chemotherapy.

Chronic myelogenous leukemia is a disease in which a very high percentage of complete remissions with disappearance of all signs and symptoms except the abnormal Ph1 chromosome can be achieved by chemotherapy with Myleran (28, 29), the drug of choice, or with other multifunctional alkylating agents such as nitrogen mustard (14), dibromomannitol (24), 6-mercaptopurine (13, 26), or hydroxyurea (41). The median survival time, however, is still 4 to 5 years, and the patients who can be kept free of disease for long periods of time without therapy are rare (58).

In chronic lymphocytic leukemia, however, this does occasionally occur, although therapy is less likely to produce complete marrow remissions with disappearance of all signs and symptoms of the disease; sometimes the disease may be controlled or may disappear entirely for very long periods of time. One such long-term survivor has been reported by A. Weisberger (personal communication). The patient’s disease was controlled by repeated therapy, and the patient has been living an active, useful life for 38 years. Chlorambucil is the drug of choice with prednisone reserved for the hemolytic or thrombocytopenic manifestations of autoimmune disease.

Acute lymphoblastic leukemia is extremely amenable to chemotherapy, and complete remissions can be achieved in approximately 90% of the patients. These are generally short-lived unless maintenance therapy is given. With the use of maintenance therapy and the development of new agents, however, the survival time of the patients with this disease has been gradually increased from the 3 to 4 months median survival time [before any treatment was available (63)] to 8 months on Methotrexate and steroids, to 12 months after 6-mercaptopurine was added (7), and now to between 18 and 30 months depending on the dose regimen that is followed (65). These children are in excellent health most of the time during the remissions, and so this therapy could certainly be considered successful. The number of patients who have survived for 5 years with no evidence of disease, however, is still low. The only large series available to date, that of Zuelzer (66), shows 4.3% of 5-year survivors.

With the various forms of intensive therapy, it is too early to establish 5-year survival rates, but of 35 children with acute lymphoblastic leukemia (ALL) treated by Henderson et al. (32) in the POMP (prednisone, vincristine, Methotrexate, 6-mercaptopurine) program, 7 of the 35 or 20% were surviving at 3 years, and 3 of the 35 or 9% were living and well at 4 years (10). Of the 21 children on large doses of intermittent intramuscular Methotrexate reported originally by Selawry (1; J. F. Holland, personal communication), 3 out of 21 or 14% show no evidence of disease 4 years or more from diagnosis (10). In a series of ALL’s treated by Djerassi (22; personal communication), using mainly high-pulse Methotrexate cycle maintenance, 13 of 52 or 25% were surviving at 3 years and 3 of 52 or 5.8% at 4 years (10). The best figures are those reported by Holland (36) for Leukemia Group B with better than 50% survivors at 2 years of the 294 patients treated by the group protocols during 1966 and 1967. With the exception of Zuelzer’s series, it is too early to determine what the 5-year survivors will be in the other series since not all of the patients in any of these series have had time to go to 5 or even 3 years. The figures which are given are of those patients who are presently surviving at those times. In all except Zuelzer’s series, more patients are alive (with no evidence of disease) who may survive to a later period. Thus, although it is still too early to compare the effect of those forms of massive therapy with that of the more conventional cyclic therapy used by Zuelzer (66), it seems likely that a larger percentage of 5-year survivors will be achieved. From the figures of the Acute Leukemia Long-Term Survival Registry, it would appear that of those patients surviving 5 years, at least 50% should remain in orbit indefinitely (9).

In 2 of these tumors, choriocarcinoma and Burkitt’s tumor, it seems likely that host defenses play a role in the achievement of long-term remissions. Choriocarcinoma is a tumor of fetal origin growing in the mother and so should be potentially antigenic (42). Patients with completely regressed Burkitt’s tumor have been shown by Klein et al. (40) to have a higher titer of antibodies against their own and allogeneic Burkitt’s cells than those patients whose disease did not respond as well. In other tumors which occasionally regress under inadequate chemotherapy or surgery, such as melanoma (53, 56), osteogenic sarcoma (52), and neuroblastoma (31), evidence has recently been presented of tumor-specific antibodies.
It has been suggested that bolstering of host defenses either passively by plasma, adaptively by immunized cells, or actively by specific or nonspecific stimuli, such as BCG or the methanol-extracted residue of BCG (MER) (64), at a time of minimal residual tumor might produce a mopping up of the few tumor cells remaining after chemotherapy and thus prevent a relapse (8). Recently, Mathé (50; personal communication) using injections of frozen irradiated allogeneic leukemic marrow or nonspecific stimulation with repeated applications of BCG, has reported some interesting but preliminary results. Of 30 patients with ALL in complete remission, 10 were taken off all maintenance therapy, and all had relapsed within 130 days. Another 20 similarly with no maintenance chemotherapy were given “immunotherapy” with either repeated applications of BCG or injections of irradiated pooled allogeneic leukemic marrow. Of these 20, 12 had relapsed, but 8 were still in remission from 297 to 1150 days after the discontinuance of chemotherapy. This type of immunotherapy at a time of minimal residual tumor might be all that is necessary to convert a potential chemotherapeutic failure into a success.

The concepts of success and failure in chemotherapy are particularly well illustrated by a new chemotherapeutic agent A-ase (4-6, 17, 19, 30, 39, 49, 54, 57, 59), which produces complete but temporary remissions in ALL, and by certain laboratory and clinical studies of this substance which attempt to convert failure into success. The latest clinical data reported by Tallal et al. (62) and by Lipton et al. (47) demonstrated an incidence of complete marrow remissions of 50 to 60% after 4 weeks of therapy in ALL regardless of the daily dose for 4 weeks over a range of from 5 IU/kg to 5,000 IU/kg daily. These remissions were temporary, however, lasting from 1 to 9 months. In acute myeloblastic leukemia of adults, there were only 4 complete or good partial remissions out of 32 patients. However, there were many more patients with acute myeloblastic leukemia who showed temporary evidence of therapeutic effect, e.g., a fall in the peripheral leukocyte count or a decrease in splenomegaly or hepatomegaly during the first week or 10 days of treatment, only to relapse again during the third or fourth week while still on the same dose of A-ase. This suggests that the induction of the enzyme asparagine synthetase by the A-ase-produced deficiency of asparagine had rendered the leukemic cell independent of asparagine.

Experimental studies in mice with advanced transplanted leukemias EARAD1 or L5178Y/CA55, however, showed that A-ase, 20 IU/kg daily for 5 days, caused regression of the leukemia and prolonged the survival but that the disease eventually came back and killed the mice, whereas large doses such as 1,000 or 5,000 IU/kg produced a significant number of 50-day cures (4, 12). If one could extrapolate from the mouse data to ALL in man, one would expect that, although 5 to 10 IU/kg daily would produce complete, temporary remissions, 1,000 to 5,000 IU/kg for 28 days should not only produce complete remissions but might also produce a very long-term remission in an occasional patient.

Preliminary studies on a small and inhomogenous group of 32 children with ALL treated with either 200 IU/kg or 1,000 IU/kg intravenously daily for 28 days showed 5/11 and 13/21 complete or good partial remissions respectively. The length of unmaintained remissions, however, was considerably longer in the 1,000 IU/kg patients, and 4 are still in remission, 2 at 7 and 8 months after the discontinuance of all therapy (Chart 2).

![Chart 2. Effect of dose of asparaginase on length of unmaintained remission in acute lymphoblastic leukemia in children.](chart2)

It seems likely that the levels of A-ase maintained in plasma and tissues are of importance in the destruction of leukemic cells. Schwartz et al.² have shown that the half-life of the A-ase supplied by Merck or Squibb was approximately 20 hours, and it was 10 hours with that supplied by Bayer. With the Merck or Squibb preparations, plasma levels of A-ase 24 hours after the previous daily dose of 1,000 IU/kg were in the neighborhood of 20 IU/ml and with 200 IU/kg approximately 5 IU/ml. Even though in leukemia L5178Y in cell culture the concentration of A-ase necessary to cause a 50% inhibition of growth over 72 to 96 hours was only 0.0001 to 0.0003 IU/ml (23), the amount necessary to sterilize the cell suspension so that it would not produce leukemia on bioassay into susceptible mice was many fold higher (10 to 100 IU/ml) and was highly dependent on time of exposure (Table 2). This in vitro cytotoxic technic takes advantage of the extremely short half-life of A-ase in the normal mouse, as contrasted to the 5-day leukemic mouse. Control studies have shown that the higher concentrations of A-ase which are in the bioassay inoculum are insufficient to produce a curative effect in vivo when given simultaneously with the leukemic cells. Thus, the bioassay of these cells into normal compatible mice is a direct assay of the cytotoxic effect of A-ase in vitro. This dependence on concentration and time of exposure suggests that any manipulation of the A-ase molecule which might increase its half-life might be of value. A new chemically modified A-ase produced by Bayer has a half-life comparable to that of the Merck preparation. Thus, this and other semisynthetic A-ase derivatives may be useful in prolonging the half-life of A-ase in in vivo studies.

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Table 2

<table>
<thead>
<tr>
<th>Incubation (hours)</th>
<th>Concentration of A-ase (IU/ml)</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5/10</td>
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<td>24</td>
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<tr>
<td>48</td>
<td>0/10</td>
</tr>
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<td>72</td>
<td>0/10</td>
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50-day bioassay survivors

Effect of time and concentration on in vitro cytotoxic activity of L-asparaginase (A-ase) on L5178Y cells as determined by bioassay. The initial inoculum was L5178Y (200,000 cells/ml) incubated at 37°C in minimum essential medium + nonessential amino acids + 15% fetal bovine serum. One ml was bioassayed and injected i.p. into each of 10 BDF1 mice at each level.

Table 3

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (Day 7)</th>
<th>Δ wt. (Day 12)</th>
<th>Survival time</th>
<th>% ILS</th>
<th>50-day survival</th>
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<td>-0.4</td>
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<td>26.6</td>
<td>+85</td>
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<td>ara-C</td>
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<td>+0.5</td>
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<tr>
<td>A-ase</td>
<td>500</td>
<td>-1.0</td>
<td>10/10</td>
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Effect of prior treatment with cytosine arabinoside (ara-C) and thioguanine (TG) on antileukemic activity of a single dose L-asparaginase (A-ase) against leukemia EARAD1 i.p. ILS, increase in life span.

Man and achieving the double goal of more effective and less frequent therapy and, perhaps, changing chemotherapeutic failure into success.

In mice with leukemia EARAD1, treatment with cytosine arabinoside and thioguanine potentiated the effects of a small dose of A-ase to a point where it produced 50-day cures (11) (Table 3). In leukemia L5178Y which is more resistant to the curative effects of A-ase than either EARAD1 or the CA55 clone of L5178Y, cures could not be achieved with A-ase alone at doses up to 5,000 IU/kg daily for 5 doses. In this leukemia, however, the addition of either vincristine at a single dose of 1 mg/kg (Chart 3) or Daunomycin 1 mg/kg daily for 5 days (Chart 4) produced a high percentage of 50-day survivors, although neither drug alone had more than a transitory effect on this leukemia.

Thus, these data in the mice point to the value of
combination chemotherapy with A-ase and several different agents in order to increase the log kill of leukemic cells. If these studies can be extrapolated to ALL of man, they might increase the success not so much in regard to the initial remission rates but rather in respect to the number of patients in whom long-term remissions could be achieved. The fact that A-ase has relatively little toxicity for the normal cells over a thousand-fold range makes it an ideal compound to use in combination with other and more toxic drugs. Such combination therapy with assistance from stimulated host defenses may make the difference between success and failure in cancer chemotherapy.

In conclusion, it is suggested that, in these few tumors that we have discussed, chemotherapy has come of age. And as the surgeons and radiotherapists have done before us, we should cease to be content with palliation and, in space-age parlance, should set as our goal blast-offs with intensive therapy which will achieve not low-trajectory, short-lived remissions but, rather, permanent, disease-free orbits.

REFERENCES


33. Hertz, R., Lewis J., Jr., and Lipsett, M. B. Five Years’ Experience

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Fig. 1. Effects of therapy on pulmonary metastases in a young male with choriocarcinoma of the testis.

Fig. 2. Effects of therapy on pulmonary metastases of embryonal carcinoma of the testis.
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