Editorial

Radiophosphorous Therapy in Polycythemia

By Baruch Modan

THE USE of P32 in the therapy of polycythemia vera has continued to be a controversial subject since it was first introduced.1-5,15 Although considered as the ultimate treatment for polycythemia vera by many hematologists it has, on the other hand, been discredited by others as being responsible for a high proportion of deaths from acute leukemia.

The main obstacle to an objective evaluation of the efficacy of P32 has been the lack of a well-controlled clinical trial. One supposes that such a study would have been conducted when this radiotherapeutic method was first introduced, but unfortunately it never was. In view of the growing skepticism regarding the net therapeutic effect of P32, it was felt that an evaluation of this kind was justified, especially because of the increasing use of radioactive materials in general. However, it seemed that for a clinical trial to be well designed, a preliminary retrospective evaluation of the presumed complications would be desirable.

A large-scale study,6 based on the past experiences of 1222 patients, with various types of polycythemia, treated in 7 different clinics and receiving different forms of treatment, was recently carried out in the attempt to determine whether patients with polycythemia vera were indeed subjected to a higher risk of developing acute leukemia and whether the increased risk was related to the P32 and/or x-ray treatment employed.

An extensive follow-up ranging from 8 to 25 years revealed a 10 per cent minimum frequency of acute leukemia among 228 P32-treated and 72 x-ray-treated polycythemia vera patients, but only 1 case of acute leukemia among 133 patients treated by means other than radiation. Leukemia frequencies of the same order of magnitude were found in a group of patients treated with P32 and in whom the diagnosis of polycythemia vera was uncertain; most of these were patients with benign erythrocytosis.7 No cases of acute leukemia were found among 301 patients in the latter diagnostic group who received no radiation. These findings led to the conclusion that ionizing irradiation bore a direct relationship to the development of acute leukemia. Further analysis disclosed that, contrary to the prevalent assumption, neither the length of survival nor the severity of the disease played a major role in the development of the leukemic process.

A no less crucial point, was the fact that the length of survival of the P32 treated patients was not found to be significantly superior to that of the ones receiving no radiation treatment. The above observation appears to be of utmost importance with regard to the argument stressed by Osgood8 that

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although radioactively treated patients have a higher risk of developing leukemia one is obliged to use this form of therapy, since one prefers the patient to die of leukemia at an older age rather than to die of thrombosis earlier. This dispute and the fervent arguments regarding the superiority of $^{32}$P treatment and its ability to prolong the life span of the polycythemic patient have not as yet reached an end point, as demonstrated by Osgood.9

At least some of the continuously pressed opinions in favor of the "better" survival of $^{32}$P-treated patients are perhaps based on an unintentional misinterpretation, first made by Lawrence,2 and subsequently repeated by Calabresi and Meyer,9 Chievitz and Thiede1 and eventually by Osgood.9 Left out in each of the above-mentioned analyses was the fact that the study groups under consideration comprised, in addition to patients treated in the initial stage of their disease, a large number of patients referred for $^{32}$P treatment a considerable period of time after their diagnosis, having been previously treated by measures other than radiation. In many cases, this was due to the simple fact that the drug had not yet been introduced at the time the diagnosis was established. Consequently, of 2 patients who were diagnosed at the same time period, the one who survived long enough to reach the "$^{32}$P era" would be included in the $^{32}$P group, whereas the one who died earlier would be counted among those who received no radiation treatment. Also, patients diagnosed at a preterminal stage would almost certainly be included in the no-radiation group. For, obviously, a patient admitted because of a severe myocardial infarction and found simultaneously to have polycythemia vera, would hardly be treated with radioactivity. Thus, the $^{32}$P category will contain a selected group of patients with relatively longer survival time than the no-radiation category.12 An exclusion of patients referred for radioactive therapy more than 1 year after diagnosis and an adjustment for some other sources of bias reduces the apparent superior survivorship of $^{32}$P-treated patients to a nonsignificant level, compared to those not so treated. Moreover, should a larger sample, or a longer follow-up period deem this difference to be statistically significant, the difference would be in the order of magnitude of less than 2 years, certainly not 7, as previously claimed.2

If one does not accept this argument, one must, by the same token, agree with the "superior" survival time of nonirradiated polycythemia vera patients, just reported by Perkins et al.15 and possibly subjected to a similar kind of bias.

It should also be pointed out that despite the relatively high proportion of deaths from acute leukemia, $^{32}$P has not been found to have shortened the length of survival of the patients thus treated, leading to the obvious conclusion that the course of the disease itself was altered, not its duration. One is therefore left with the dilemma of either continuing to employ radioactive substances, accepting the increased risk of leukemia, or shifting towards other therapeutic agents, accepting a supposedly increased risk of thrombotic events, and of other possible disturbances that have been insufficiently studied.

An objective assessment of the outcome of $^{32}$P treatment must also take
into account the beneficial effect of regular visits to a large medical center. This factor would obviously have much more weight in the P32-treated group than in the nonradioactively treated. At present no information is available as to the relative contribution of a close medical supervision, when combined with conservative therapeutic measures, on the course of polycythemia vera. The current considerably large series of nonradioactively treated patients that do benefit from a regular and thorough follow-up, like the N. Y. Mount Sinai Hospital's Chemotherapy group,13 or the one treated by phlebotomy alone at Johns Hopkins,14 to name just a few, will, hopefully shed some additional light on this problem, and provide invaluable information about the terminal stages of the disease.

The only way to solve a problem of this kind conclusively, would be through a well-designed randomized clinical trial. But, once again, one is faced with the problem of convincing the physician who relates the leukemogenic outcome of polycythemic patients to P32 therapy to treat one-half of his patients with the drug, and asking the physician who almost religiously believes in the curative superiority of P32 to withhold it from one-half of his patients. Both will consider the request unethical since we have no real guidelines whether it is more prudent to take the risk of treatment or to refrain from it.

On the other hand, there always exists the ethical question as to the extent to which we should, as physicians, proceed with the treatment of one disease, given the danger of leading iatrogenically to a second disease. In face of the available evidence, one feels inclined to become more cautious with regard to the employment of radioactive substances in polycythemia. Needless to say, the discontinuance of a drug that was considered miraculous only a few years ago and that is still most popular with leading centers, seems very difficult. But, it should be realized that one of the unfortunate outcomes of the popularity and wide acceptance of any therapeutic agent would be the decrease in the efforts for discovery of a suitable substitute.

We are therefore left with the conclusion that even while the answer to the exact quantitative aspect of the effect of P32 is still pending, we cannot but feel that the high hopes associated with this substance have not been fulfilled and that further research with the aim of seeking a more biologic solution is still needed.

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