

1

INTRODUCTION*Kenneth D Bagshawe*

It is just 100 years since Marchand[1] identified choriocarcinoma as a tumor arising from placental villous trophoblast. Earlier descriptions of similar tumors had failed to identify their tissue of origin. Gestational trophoblastic disease (GTD) is the terminological umbrella now used to span the spectrum of cellular proliferations ranging from the various forms of hydatidiform mole through invasive mole and choriocarcinoma to placental site tumors[2]. Each form of GTD presents its own particular set of problems ranging from social to therapeutic.

These proliferations are unique in several respects. In the first place, there is no known homolog of hydatidiform mole in any other species although this could possibly be masked by maternal placentophagy. The rare identification of choriocarcinoma-like tumors remains restricted to a rhesus monkey[3] and an armadillo[4]. In the human, histologically characterized choriocarcinoma behaves in a broadly similar fashion whether it is genetically identical with the host as in a germ cell origin, or whether it arises from a normal conception or an androgenetic hydatidiform mole.

Gestational trophoblastic tumors have long been regarded as naturally occurring allografts in the maternal host as befits their fetal origin. At the same time the low incidence of fetal involvement by choriocarcinoma following term delivery remains unexplained. Whether they are allografts or not depends on the precise definition of allograft. Mammalian evolution has depended on the failure of the maternal immune system to reject the fetus and on the unique role of trophoblast. Thus, gestational trophoblastic tumors have a normal set or a complete set of paternal genes and it was assumed for some years that they and normal trophoblast expressed paternally derived antigens of the human leukocyte antigen (HLA) system. Evidence mounted during the 1960s and 1970s that this was not so. Further work [5] has confirmed this and shown that HLA G expression by trophoblast is a unique mechanism for abrogating immune rejection. It may be a reasonable assumption that trophoblastic tumors inherit this mechanism so that immune mechanisms are unlikely to account for their sensitivity to cytotoxic chemotherapy.

It is now more than 35 years since the sensitivity of invasive mole and choriocarcinoma to cytotoxic drugs was first recognized[6]. They remain the most sensitive and most curable of all human cancers. Apart from speculation about the contribution of the immune response to this sensitivity there has been little expression of interest as to why choriocarcinoma should, in most cases, be so responsive.

It is an issue that is not without relevance to the understanding of cytotoxic action in human cancer in general. It is probably facile to

attribute the responsiveness simply to a low propensity to drug resistance and indeed drug resistance can develop in choriocarcinoma and placental site tumor, particularly where inappropriate treatment is given. On the other hand, multi-drug resistant invasive mole has not, to my knowledge, been described.

It was suggested[7] that a progressive reduction in a tumor cell population could only be achieved with conventional cytotoxic chemotherapy under certain conditions. Tumor growth results from the fact that cell losses are less than cell gains but the margin between losses and gains varies substantially between different cancers. The analysis was based on an antimetabolite such as methotrexate and assumed that cytotoxic action was intermittent and the duration of each administration or set of administrations was determined by the sensitivity of one or more normal cell renewal compartments. In general, drug exposure time is shorter in duration than the rest phase between successive drug exposures. Further, it was proposed that the rate of cell kill was related to and limited by the size of the growth fraction of the tumor cell population, i.e. the fraction of cells in cycle. If these assumptions were justified then it was argued that the rate of spontaneous cell loss from natural causes is critical to progressive reduction in the tumor cell population. That is to say the cytotoxic drug-induced cell kill plus the spontaneous loss rate in the tumor cell population can in the course of a complete treatment cycle exceed the rate of tumor cell accumulation in the rest phase.

It will be noted that the vulnerability of normal renewal cell populations derives from the fact that over a period of time spontaneous losses equal cell additions. In contrast to tumors, normal renewal cell tissues are organized for rapid recovery from toxic insults.

The thesis is therefore that choriocarcinoma is curable because the magnitude of spontaneous losses approaches that of cell gains. Losses and gains are not readily quantifiable although this may now be a lesser problem than when the proposal was first made. Supporting evidence for a high rate of cell loss in choriocarcinoma is evident in the relatively small number of viable cells present in comparison with the total tumor mass. The intravascular cells and perivascular location of choriocarcinoma cells suggest they may be unusually vulnerable to anoxia and hence growth occurs only in close proximity to the capillaries at the periphery of tumor masses. A second and perhaps critical mechanism is the differentiation of a proportion of the stem cell population of cytotrophoblast in syncytium which is an 'end' cell. Mitoses are rarely, if ever, to be found in syncytium and these cells appear to be short-lived, so this constitutes a substantial exit route from the clonogenic population.

A personal unpublished observation is that the amount of syncytium seen in autopsy material from drug-resistant choriocarcinoma is less than that seen in pre-chemotherapy material. This could be the subject of formal study. It is also relevant that placental site trophoblastic tumor which is more frequently drug-resistant than gestational choriocarcinoma shows markedly less syncytium formation.

The implication of the suggestion that the natural cell loss rate

from a tumor is critical to its response to conventional cytotoxic therapy is that complete responsiveness is inherent in the biology of some tumors but not, unfortunately, in the majority of common cancers. If this were to be proven it would challenge the widely held view that the failure of cytotoxics to be curative of common cancers is the result of natural or acquired drug resistance at the biochemical level. Whilst this undoubtedly occurs, the correlation between drug resistance at the clinical and biochemical levels does not appear to be supported by a substantial body of evidence.

I have dwelt on this subject at some length because some of the motivation in the early years of chemotherapy for trophoblastic tumors was the hope that it would point the way towards the curability of more common tumors. However, curability with conventional cytotoxic therapy may be dependent on the biology of the tumor.

There was also the hope, even the expectation, that tumor markers comparable to human chorionic gonadotropin (hCG) would be found for many other cancers. Whilst there has been a proliferation of tumor-associated antigens none of them, except perhaps α -fetoprotein in some germ cell tumors, provide information comparable to that provided by hCG for trophoblastic tumors.

The screening programs for persistent trophoblastic disease following evacuation of hydatidiform mole have been instrumental in the near elimination of fatalities from the sequelae to mole and have done so at low cost. The fact that there are wide differences in intervention policy resulting in a three- to four-fold difference in the frequency of intervention is less important than the fact that the different policies are successful. If the more frequent intervention in the USA results, as has been suggested, from a fear of litigation over late intervention, perhaps unnecessary intervention will become equally persuasive in time.

The evolution of knowledge about hCG has been sustained now for almost 70 years and it continues to evolve, as does the methodology for its detection. Nothing illustrates this better than a comparison of the rarely available biological pregnancy tests with toads, mice and rabbits in the 1950s to the present time when 'over-the-counter' pregnancy tests are universally available. Nevertheless, the methodology of assays is of critical importance and many, indeed most, of the commercial sandwich assays are inferior for monitoring purposes[8] to long established radioimmunoassays employing polyclonal antisera.

The 1970s witnessed two major developments. The first was identification of etoposide as the most powerful drug so far in the assault on trophoblastic tumours of both gestational and non-gestational origin - within a few days of witnessing the drug's effect on hCG levels indicated that a long standing road block could be overcome. Patients with tumours resistant to previous multi drug therapy went into remission. Until then only about two thirds of patients achieved eradication of the disease but thereafter tumour eradication became something better than 90% in the gestational cases and with a comparable improvement in those with non-gestational disease. That this coincided with the development in ultrasound,

computerised tomography and magnetic resonance imaging meant we were closer to the objective of eliminating death from this group of diseases.

Although these new developments surpassed the use of radiolabelled antibodies directed at hCG for diagnostic purposes, such studies were at the forefront of the later development of armed antibodies in the wider fields of cancer and directed at a wide range of newly identified cell surface markers.

Although in 2015 we still await substantial evidence for the efficacy of antibody-drug conjugates they have certainly broadened the basis of the therapeutic attack.

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