Schistosomiasis - cancer : etiological considerations : a review

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Schistosomiasis – cancer: etiological considerations

A review

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Summary

Evidence for a causal connection between Schistosoma haematobium-infection and carcinoma of the urinary bladder is discussed. A group relationship of schistosomiasis cancer to cancers associated with asbestosis, foreign body implants, and cicatrization is suggested on the basis of several criteria. Results of experimental foreign body tumorigenesis in mice are presented and elaborated in relationship to schistosomiasis cancer. Carcinogenic development at the cellular level is discussed with emphasis on the essential role of tissue-environmental conditions, especially fibrotic changes and macrophage quiescence.

Key words: schistosomiasis; urinary bladder cancer; foreign body tumorigenesis.

I. The association of Schistosoma haematobium infection and urinary bladder cancer

A causal relationship between Schistosoma haematobium infection and cancer of the urinary bladder has been suspected since the turn of the century (Goebel, 1905) and can hardly be refuted in the face of mounting circumstantial and experimental evidence.

1. *Epidemiology.* – The frequency of bladder cancer is significantly increased in endemic areas of Schistosoma haematobium. In Egypt, where a large segment of the rural population is known to be infected, carcinoma of the bladder ranks first among all types of cancers recorded in males (Elsebai, 1977). Regionally, there is a correlation between the occurrence of bladder cancer and the prevalence of diffuse schistosomal bladder calcifications as detected by X-ray screening of the general population (Gelfand, 1972).

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2. *Cancer age and estimation of cancer latency.* – The incidence of bladder cancer in schistosomiasis patients peaks during the age of 30 to 50 years (Elsebai, 1977; Gelfand, 1972) whereas bladder cancer without underlying schistosomiasis is rarely encountered before the age of 50.

Schistosomal infection is commonly contracted in endemic areas during childhood. The hematuria of advanced schistosomiasis usually commences during the second decade of life. Accordingly, it can be surmised that the latency of schistosomiasis-associated bladder cancer ranges between 20 and 30 years.

3. *Anatomical site.* – Schistosomiasis-associated carcinomas may be found throughout the bladder, often at multiple sites, but especially in the posterior wall. It appears significant that they are rarely located in the trigone (Elsebai, 1977) which is a frequent site of non-schistosomiasis cancers.

4. *Macroscopic appearance.* – Bladder carcinomas in schistosomiasis have in about 80% of the cases a nodular, fungating appearence, often with a firm, solid, keratinized surface; verrucous or papillary growth is rarely observed (Elsebai, 1977). In contrast, most non-schistosomiasis cancers of the bladder present as papillary lesions with soft, friable, highly vascularized surfaces.

5. *Histopathology.* – The great majority of schistosomiasis cancers (75%) are squamous carcinomas, often with marked keratinization; transitional cell carcinomas are found in only about 20% and adenocarcinomas in 5% (Elsebai, 1977). This is in striking contrast to non-schistosomiasis carcinomas which are of the transitional cell type in over 95%.

6. *Metastasibility.* – Unlike transitional cell carcinomas which predominate in the non-schistosomiasis cases, a relatively low tendency to metastasize is initially observed in squamous schistosomiasis carcinomas. Pelvic lymph node involvement can be documented in only 20 to 30% of such cases at the time of primary surgery (Elsebai, 1977). Nevertheless, regrowth originating from the pelvic region occurs in many cases after radical cystectomy despite thorough dissection of pelvic lymph nodes. At this advanced stage development of metastases in the bones, lung, liver, etc. must be expected as a rule (Elsebai, 1977).

7. *Experimental schistosomiasis cancer in animals.* – Numerous attempts to produce cancer experimentally in non-primate animals such as rats or mice by incorporating schistosomal eggs or by inducing schistosomal infection have been unsuccessful (Al-Hussein and MacDonald, 1967; Shimkin et al., 1955). However, recently such experiments were carried out with positive results in various species of non-human primates (Kuntz et al., 1972). In this investigation, one talapoin and one capuchin monkey developed cancer of the bladder upon percutaneous cercarial infection. In uninfected control monkeys no spontaneous bladder cancers were recorded nor have such cases been reported in the literature (Kuntz et al., 1972). It is interesting to note that the findings in monkeys were not entirely identical with those in man. Most surprisingly, the latency between infection and cancer detection was very short in the two animals, namely ½ and 1 year respectively. Furthermore, both tumors were papillary in

appearance and histopathologically of the transitional cell type. Larger numbers of cases are obviously needed before any generalizations can be made regarding differences between schistosomiasis cancers of man and monkeys. Nevertheless, the experimental results support the thesis of a causal association of schistosomiasis and cancer of the urinary bladder.

II. The pre-cancer tissue reactions around schistosomal eggs

Eggs are released from adult worms lodging in the venules of the vesical and pelvic plexuses. On their way towards the mucosal surface of the bladder many of the eggs get permanently stuck in the muscular layers of the submucosa either solitarily or clustered. The tissue reaction against trapped eggs is generally that of a nonspecific chronic foreign body reaction (Felsenfeld, 1965; Gazayerly et al., 1971; Maegraith, 1971; Manson-Bahr, 1968) which shows no tendency to resolve because of the poor biodegradability of the egg shells. Yet, the eggs can not be regarded entirely inert. By means of immunofluorescence it was demonstrated that soluble material with specific antigenicity is released from young, viable ova through submicroscopic pores in the shells (Boros and Warren, 1970). This probably explains the histopathological observation of periovular micronecroses during the initial phase of the disease. But soon the necrogenic virulence of the soluble egg material vanishes, apparently due to specific intervention by cell-mediated immune mechanisms (Boros and Warren, 1970; Lichtenberg et al., 1971). The tissue now reacts more proliferatively with an influx of macrophages, giant cells, lymphocytes, and expecially eosinophils. The result is the formation of the classical "bilharzial granulomas" or "pseudotubercles" which are about 1 to 2 mm in diameter. The granulomas tend to coalesce into larger nodules and further expand into polyps, warty papillomas, or plateau-like masses which contain numerous ova. Papillomatous folds are usually encrusted by concretions of uric acid and oxalates, later augmented by phosphatic deposits. The transitional epithelial mucosa in the affected areas may become atrophic in some spots, but generally shows hyperplasia in that it both thickens and grows downward into the tunica propria. Squamous metaplasia with hyperkeratosis, resembling leukoplacic patches, is very frequently seen. Especially these latter changes may represent the precursor events that lead to cancer after many more years. Indeed, the squamous nature of the metaplastic changes seems to foretell the characteristic histopathology of most later carcinomas.

With time, the dead ova calcify and the foreign body-reactive tissue becomes predominantly fibrotic due to pronounced fibroblastic proliferation and collagen formation. The vascular network thins out as capillaries and small vessels obliterate. The resulting ischemia may cause epithelial atrophy, visible as "sandy patches" over fibrous plaques especially in the trigone. Even frank mucosal necrosis may occur leading to ulcerations with the egg-laden muscu-

laris as the base. It should be noted, however, that schistosomal carcinomas have never been seen to originate from sandy patches or ulcers (Elsebai, 1977).

The end stage of the fibrotic tissue reaction in schistosomiasis is cicatrization which causes severe contracture of the bladder and strictures of urethra and ureters. Extensive calcifications throughout the bladder wall are readily detectable on X-ray. Secondary bacterial infections of the bladder and the hydronephrotic kidneys are now a common and usually the terminal complication. This then is also the time when the incidence curve of carcinomas begins to rise.

III. Other cancers similarly associated with chronic foreign body reaction and/or fibrosis

The carcinogenic association of schistosomiasis with chronic foreign body reaction and fibrosis is not unique. Several other cancers can be linked to similar pathological preconditions.

Asbestosis-cancer is the prime representative of this category (Selikoff et al., 1964, Selikoff et al., 1968; Stell and McGill, 1973; Timbrell, 1973). Upon inhalation or ingestion, asbestos fibers penetrate through the alveolar walls or the intestinal mucosa. Like schistosomal eggs they "move" through the tissues until they are walled in by fibrous connective tissue. In the lung, this leads to extensive diffuse fibrosis of the interstitium and especially of the pleura. After latency periods of several decades, pulmonary, laryngeal, and gastro-intestinal carcinomas as well as mesotheliomas of the pleura and the peritoneum are seen to arise.

Fiber-carcinogenesis. – Asbestos fibers are known for their pronounced adsorptive surface properties (Harington, 1973). They are, because of their size and shape, also capable of penetrating through cell membranes. It was therefore theorized that asbestos fibers serve merely as vehicles for chemical carcinogens. However, critical investigations have shown that even in the absence of any detectable chemical carcinogen asbestos fibers retain their carcinogenic capacity (Stanton and Wrench, 1972; Timbrell, 1973). It is rather the size of the fibers that is of crucial importance. The highest degree of carcinogenicity was recorded for straight fibers measuring less than 3 μ in width and more than 20 μ in length (Stanton et al., 1977). With these dimensions many different kinds of fibrous materials were proven to be carcinogenic in animals upon injection into the pleural spaces or the peritoneal cavity. Such tests were performed with fibers of glass, aluminum oxide, silicon dioxide, barium sulphate, magnesium hydroxide, and others (Stanton, 1974; Stanton et al., 1977). Consequently the term "fiber carcinogenesis" was coined (Stanton, 1974). A regular and common histological finding during the preneoplastic stage of fiber carcinogenesis is marked tissue fibrosis (Stanton et al., 1977).

Tobacco-smoking as a carcinogen may be related to this category of cancers directly or indirectly. The role of smoking in the development of lung cancer

seems indisputable. Moreover, the incidence of asbestos cancer is almost 100 times greater in smokers than in non-smokers (Selikoff et al., 1968). The chemical carcinogenic components in tobacco smoke are well defined. However, smoking also stimulates and promotes nonspecifically interstitial fibrosis around irritated and damaged bronchioli. Thus, smoking may independently create a state of carcinogenic fibrosis, or its effect may be additive to other fibrogenic stimulants such as asbestos.

Scar-cancers have been reported to occur in various organs after latencies averaging between 20 and 30 years without specific relationship to the cause of such scars (Ott, 1970).

In the lung, interstitial scarring from old tuberculous lesions, infarctions, pneumoconioses, or embedded foreign bodies often causes hyper- or metaplasia of the alveolar epithelium from which bronchiolar-alveolar adenocarcinomas (85%) or less frequently squamous carcinomas (10%) may arise (Ripstein et al., 1968). The predominance of bronchiolar-alveolar adenocarcinomas in association with cicatrization is statistically significant in view of the fact that usually the pulmonary carcinomas are of the squamous type.

Originating from fibrous pleura adhesion, 6 cases of highly differentiated keratinizing squamous cell carcinomas were recently reported following extrapleural pneumolysis for pulmonary tuberculosis in 121 patients (Willén et al., 1976).

Skin neoplasms are also known to occur in scars resulting from deep burns (Lawrence, 1952) or gunshot wounds (Guslitser, 1963; Ott, 1970).

Finally, reports should be mentioned which suggest that some breast cancers may be causally associated with surgical or postinfectious scars (Freund et al., 1976; Ripstein et al., 1968).

Cancer at sites of artificial implants or accidental foreign bodies. – Numerous reports have appeared in the medical literature which document the occurrence of neoplasms, mostly sarcomas, in humans as a consequence of chronic fibrous foreign body reactions around extraneous materials lodging in the tissues for some decades. Materials incriminated in these cases include corrosive metals such as gunshot bullets or shrapnel fragments (Ott, 1970), stainless steel plates for bone repair (Dube and Fisher, 1972; McDougall, 1956; Maltoni et al., 1974), polymer plastic vascular grafts (Burns et al., 1972, O'Connell et al., 1976), and others (Bischoff, 1972; Ott, 1970; Thompson and Entin, 1969; Zafiracopoulos and Rouskas, 1974).

IV. Experimental foreign body tumorigenesis in mice

As was indicated earlier, the commonly available laboratory animals are not suited for the study of schistosomiasis cancer if one wishes to simulate the natural course of pathogenic events at the appropriate organ site. However, the experimental model of subcutaneous foreign body tumorigenesis in mice has

proven useful for the elucidation of aspects related to the group of cancers which are etiologically associated with chronic foreign body reaction and/or tissue fibrosis.

First of all, it has been established beyond any doubt that the physical presence and nature of the foreign body (FB) material, not its chemical reactivity, are responsible for tumor development (Bischoff and Bryson, 1964). Many investigators have further studied the histology of tissue reactions in different animal species in response to FB-implants of different sizes, shapes, or surface properties (Brand et al., 1976). The results indicated that tumor incidence was strongly influenced by the type and course of the FB-reactions. The degree of fibrotic encapsulation of the FB and a chronic course of the FB-reaction were positively correlated with FB-tumor incidence.

The investigations in our laboratory were based on the following experimental design (Brand et al., 1967). Plastic films (unplasticized vinyl chloride vinyl acetate copolymer or other inert materials, $15 \times 22 \times 0.2$ mm in size) were implanted subcutaneously in CBA/H or CBA/H-T6 mice. After various time periods, the implants covered by firmly adhering FB-reactive cells were excised and cut into 7×15 mm segments. These were transferred separately to recipient mice of the other substrain being fully histocompatible yet distinguishable from the donor mouse on the basis of the T6-marker chromosome. Sarcomas of donor origin as proven karyologically developed in the recipients up to 2 years later, indicating that preneoplastic cells resided on the FB-surface at the time of transfer. In other experiments, FB-reactive capsules around implants were partly excised and likewise transferred for the purpose of establishing the presence of preneoplastic cells. FB-reactive tissues at the time of excision and transfer as well as tumors were studied histologically, karyologically, immunologically, and also by in vitro culture. The tumors, in addition, were examined for growth characteristics and transplantability in vivo.

Our main results can be summarized as follows (Brand, 1975; Brand, 1976a; Brand, 1976b; Brand et al., 1976). FB-induced tumors are true sarcomas of varied histopathology and anaplasticity; they are transplantable and grow invasively. Varied chromosomal aberrations are a regular finding. Tumor-specific transplantation antigens are detectable neither in the tumor cells nor in tumor-precursor cells during preneoplasia; immune surveillance is not operative in FB-tumor development (Michelich et al., 1977); histocompatibility antigens are frequently lost in FB-tumor cells as well as in precursor cells during preneoplasia (Brand et al., 1972).

Tumors that arose from segments of the same original implant were usually identical or closely related ("homologous") in various criteria:

a) regarding tumor latency, in that neoplastic growth commenced in all recipients at closely spaced moments in time;
b) regarding specific karyological aberrations, in terms of number and morphology of chromosomes;

c) regarding histopathology, in terms of sarcoma type and degree of anaplasticity;
d) regarding growth characteristics and cell generation times in vivo and in vitro.

These findings pointed to the clonal nature of tumor precursor cells and thus implied the prior existence of "parent" cells. Extended studies suggested that parent cells are derived from mesenchymal stem cells of the microvasculature, probably pericytes. The number of preneoplastic parent cells evoked by an implanted FB is relatively small dependent on the size of the FB. (The "Most Probable Number" of parent cells is 1.0 in response to subcutaneous implantation of a $15 \times 7 \times 0.2$ mm plastic film in CBA/H mice).

Clone-splitting and transfer experiments at various times showed that preneoplastic cells emerge already during the earliest stage of the tumorigenic FB-reaction, i.e. within 4 to 8 weeks following initial FB-implantation. At this time neoplastic destination and specific determinants of the later tumors (such as latency, histopathology, chromosomal aberrations, etc.) can already be recognized as stable properties of the preneoplastic cells. Most significantly, it was ascertained that the preneoplastic cells had not come into contact with the FB-surface at this time. Consequently, the FB being neither cell-invasive nor in the position to exert a direct membrane-mediated effect can not be considered the primary element in creating the basic cell abnormality which initiates the carcinogenic process.

The timing of this experimentation was extended over the entire preneoplastic period. The results revealed that FB-carcinogenesis is essentially a multistage developmental process depending on a stringent sequence of tissue-environmental conditions. The period which we define as "Stage one" begins with the implantation of the FB followed by acute inflammatory FB-reaction with cellular infiltration predominantly by macrophage-type cells. The FB-surface is covered by a macrophage-monolayer already by the 12th day. As previously pointed out, within 4 to 8 weeks specific preneoplastic cells can be demonstrated in the loose cellular FB-reactive tissue, but not on the FB-surface among the monolayer cells. "Stage two" is characterized by the gradual formation of a fibrous collagenous capsule around the FB during the second month postimplantation. Preneoplastic cells are now present as clones in the capsule and in the loose connective tissue around it, but still not on the FB-surface. Various experimental manipulations make it possible to prolong the dominance of inflammatory cells and thus decelerate the fibrous conversion of the FB-reactive tissue. As a result, the appearance and expansion of preneoplastic cells is delayed. "Stage three" begins when preneoplastic clonal cells settle on the FB-surface. The timing of this event varies. It usually occurs between the 5th and the 7th month postimplantation. During this period the fibrotic consolidation of the capsule comes to completion while the vascularization is appreciably reduced. Macrophage-type cells still predominate in number on the FB-surface

but appear ultrastructurally inactive and dormant. The condition of a chronic stationary FB-reaction was shown to be an essential prerequisite for preneoplastic progression. Experimental interference with this state of tissue quiescence, e.g. by implanting a FB with roughened rather than smooth surfaces, delays or even aborts the intracellular process of preneoplastic "maturation". The final acquisition of neoplastic autonomy at "Stage four" is greatly facilitated when the preneoplastic cells are firmly attached to the FB-surface. Obviously, the cell-membrane assumes a crucial role during this terminal step of the carcinogenic process. Unattached clonal sister cells which we were able to study separately during this stage rarely become fully cancerous. In fact, after removal of the FB usually these cells were either reverted or possibly eliminated by the restored controlling forces in the normalized tissue.

V. Concluding discussion

A number of hypotheses have been proposed on more or less speculative grounds to explain the etiological role of schistosomiasis in the development of bladder cancer. It is interesting to note, but certainly not surprising, that virtually the same hypothetical ideas have emerged independently in connection with the various other forms of cancer which we have grouped together here as etiologically related. Among others it was suggested that fibrotic tissue contracture causes blockage of lymphatics and thus allows carcinogenic chemicals or metabolites to accumulate (Elsebai, 1977; Ripstein et al., 1968). Decreased blood supply and tissue anoxia due to vascular obliteration was believed to be carcinogenic either primarily or by slowing the transport of carcinogenic substances and metabolites (Freund et al., 1976). Further it was hypothesized that impairment of cell membrane functions due to direct physical contact of cells with foreign particles could bring about the carcinogenic key event (Bischoff and Bryson, 1964). The results of experimental foreign body tumorigenesis enable us now to appraise previous hypothetical suggestions more critically. Especially the following results appear crucial:

1. The cancer-determining abnormality occurs in cells distant from the foreign body and prior to fibrotic encapsulation of the foreign body area.
2. The foreign particles need not be cell-invasive for causing cancer.
3. Presence or involvement of chemical carcinogens is nonessential.
4. Fibrotic tissue conditions and cell membrane disturbance are indispensible for preneoplastic progression.

Accordingly, some of the above-mentioned hypothetical ideas may apply to the advanced stage of preneoplastic progression, but they do not explain the primary carcinogenic key event.

Despite their etiological similarities, the cancers which we have discussed as a closely related group show certain differences especially with regard to histopathology. Whereas foreign body-induced cancers in mice or man are

mostly sarcomas, the cancers associated with schistosomiasis are carcinomas. Asbestos produces both kinds depending on the site where fibers have accumulated the most and reactive fibrosis is the strongest. Moreover, different histopathologic types are seen within the classes of either carcinomas or sarcomas as was pointed out before. These observations seem to indicate that, although the etiological circumstances are similar, the cell type of origin differs. In experimental FB-tumorigenesis, the originator cell was shown to be most likely derived from vascular pericytes. Schistosomiasis cancer seems to develop from the transitional epithelium of the bladder, asbestosis cancer from either the columnar epithelium of the bronchioli or from the mesothelial lining of the pleura. However, even when a common cell type of origin is involved the ultimate cancer histopathology may still vary as in experimental FB-tumorigenesis where hemangio-, fibro-, myxosarcomas and other types occur, or in schistosomiasis cancer where we see both squamous and transitional cell carcinomas. We must, therefore, conclude that the cancers originate from stem cells or from predifferentiated regenerative cells which have preserved the capacity to differentiate in various directions or, if they follow their normal differentiation pathway, are set to reach abnormal endpoints.

The nature of the primary carcinogenic key event which causes the basic cancer-determing cell abnormality is obscure. However, according to the results of experimental FB-tumorigenesis neither chemical nor physical cell-directed forces are operative in bringing the key event about. Instead, we seem to be dealing here with a spontaneous intrinsic occurrence. It appears significant that it is probably the stem cells or pre-differentiated cells which are afflicted. This is consistent with the notion that the genomes of stem cells are kept in an unstable condition beyond embryogenesis in order to preserve pluripotentiality and variability of differentiation (Scarano, 1971). For this essential property stem cells may have to pay a price which is susceptibility to spontaneous genomic errors, especially during forced proliferation (German, 1973).

The cancers under discussion may differ furthermore regarding the disease stage during which the carcinogenic key event takes place. In experimental FB-tumorigenesis it occurs early during the acute foreign body reaction at the time of cellular proliferation and vascular sprouting, but prior to fibrous conversion. In schistosomiasis or asbestosis it may occur much later, presumably in connection with epithelial metaplasia which develops in response to chronic submucosal granulomas or interstitial fibrosis. Conceivably, fibrotic changes create tissue conditions which generate altered induction signals and thus distort the epithelial differentiation process.

The results of experimental FB-tumorigenesis further show that tissue fibrosis coupled with macrophage inactivity continues to direct the carcinogenic process by promoting intracellular preneoplastic maturation. Besides continuance, the extent and distribution of tissue fibrosis seem to be critical. Widespread diffuse fibrosis as in asbestosis and advanced schistosomiasis is associat-

ed with high cancer incidence, in contrast to the more localized nodular fibrosis in pulmonary silicosis. It is obvious that tissue-environmental factors can commandeer intracellular processes only through transmembranous communication, which emphasizes the importance of the cell membrane at this stage.

The suggestion that fibrosis creates immunologically privileged pockets allowing cancer cells to evade the immune surveillance mechanisms of the body (Freund et al., 1976) appears irrelevant. In foreign body-induced cancer cells no tumor-specific transplantation antigens were demonstrated in effective amounts; in fact, most tumors had lost normal histocompatibility antigens (Brand et al., 1972; Michelich et al., 1977).

During the terminal step towards neoplastic cell autonomy the involvement of the cell membrane becomes even more crucial. As FB-tumorigenesis experiments have shown, impairment of membrane function by cellular attachment to a solid surface facilitates and accelerates the completion of the carcinogenic process. Effective surfaces may be provided in tissues not only by extraneous materials, but also by mineral deposits or firm collagen.

In conclusion, there remains little doubt that Schistosoma haematobium infection causes cancer of the urinary bladder. As deduced from observation and experimentation, the factor of central importance is the chronic fibrotic foreign body reaction in the bladder wall against schistosomal eggs. It forces and misdirects epithelial proliferation into abnormal hyper- and metaplasia. A spontaneous genomic error in the regenerative pre-differentiated cells of the disorganized epithelium may constitute the initiating carcinogenic key event. Chemical factors if present in the tissue environment may conceivably participate in bringing the key event about. However, chemical co-carcinogenesis is not believed to be an essential prerequisite. Preneoplastic cellular progression during cancer latency, which may last for several decades, depends on continued tissue fibrosis. The final attainment of neoplastic autonomy seems to involve the cell membranes. These may be affected directly by the surfaces of calcified ova, mineral deposits, or collagen.

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