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Thrombophlebitis Migrans and Malignancy

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Introduction

The treatment of Cancer is far from being satisfactory. It cannot be eradicated without the damage of the normal and healthy parts. It is usually destructive to the healthy tissue, and often to the whole individual, excision by surgery or destruction by chemotherapy and radiation, weaken the immune system of the body and often do more harm than good. The treatment of Cancer is either by surgery with wide excision or chemotherapy or both. Both methods of treatment are destructive to the individual with no sure of guarantee of cure. It will be explored in the manuscript, the nature of the tumor and its specific antigens and the response of the body by cellular and humoral antibodies. It is discussed that the antibodies respond by two types of reaction, by destruction or by coating and protection of the cancer cells or by interfering with the antibodies that are specific and toxic. That is to say, that there are types which enhance the growth of the malignant cells and interfere with its destruction by the immune system of the body.

Searching for a better method of cure is always the goal of every treating physician and immunotherapy comes in the forefront of the list. It is a safe method of treatment and can be combined with conservative surgical excision, which may be required to decrease the antigen load. Limited surgical excision decreases the antigen load and avoids any damage to the healthy tissue. It also increases the possibility of complete cure when combined with the immunotherapy.

Thrombophlebitis migrans, which manifest its self often, in several autoimmune disorders and tissue transplantation, is a sign of the body's attempt to reject different tissues that carry different antigens. In autoimmune disease, the immune system fights its own tissue that acquire different antigen or undergo mutation of its own cells. It is an important subject that relates some types of thrombosis to certain types of malignancy. The relation is important as it is an immunological reaction that can be very useful and safer weapon for treatment, if not complete cure of cancer. The chemotherapy is a more dangerous treatment, since beside its destruction to the malignant cells, it destroys the normal tissues, and in particular the immune system.

The discussion in the manuscript focuses in establishing an immunological link between the cancer and the thrombosis, which in turn start the process of rejection and immunological excision. Thrombosis has an immunological origin, to destroy the malignant cells, or can be made so. The presence of different antigens in the tumor is discussed and the ability of the body to produce specific antibodies to destroy and neutralize each of them is explained. Increasing the gap between the antigen {tumour} and the antibody may be a stronger stimulating force to destroy the cancer. The immune cells manipulated and even tailored to be a potent weapon, and an effective remedy for the treatment or even the cure of the patient from his malignancy. Finally a comparison made by the tumor syngraft and the allograft, which confirm that the allograft rejection is applicable to tumor syngraft. The last few pages are devoted to allograft rejection, and this satisfies the reader that tumor cure by immunotherapy…….

Thrombophlebitis and Cancer

Trousseau, in 1859 [1] called attention to the association of thrombophlebitis migrans and carcinoma of the internal organs. He pointed out that phlebitis may be a possible sign of hidden cancer.

It is a historic tragedy that the carcinoma of the stomach which was the cause of his death first called attention to its self by an episode of thrombophlebitis [2].

It was not until 73 years later that Sproul [3] reviewed 4258 autopsies. She found that 31%of the cases of the pancreas, especially the body and the tail, were associated with multiple thrombophlebitis. Cancer of the stomach came next in frequency. Only 2.5% of the cases of bronchiogenic were associated with venous thrombosis and the cause was thought to be either infiltration or complete obstruction of the pulmonary veins with malignant cells.

Liberman [4] found that bronchiogenic carcinoma of the male and genital carcinomas in the female were the commonest tumor associated with thrombophlebitis. Other tumours have occurred in association with venous thrombosis, such as Hodgkin's disease and multiple myeloma.

The relation between the development of thrombophlebitis and the clinical diagnosis of carcinoma is variable. In many cases thrombophlebitis developed before a diagnosis of cancer could be made [5 - 9]. In Libermans series thrombophlebitis was recognized in 31 of 51 patients prior to the discovery of carcinoma. The time interval varied between two month and more than one year. In a series from Mayo clinic, the thrombophlebitis was present.

At the initial examination in 26 of 27 patients with malignancy and was the first symptom of the disease in 14 patients. The average time interval until definitive diagnosis was about 4 months.

Thrombophlebitis often has an atypical distribution [2, 4, 8] however the veins of the extremities both super facial and deep are usually involved. The veins may also be involved in the abdominal cavity, the neck and the cavernous tissue of the penis. Some cases are associated with non-bacterial vegetation over the aortic valves [4, 10].

One additional important feature of this type of thrombosis is its resistance to anticoagulant therapy [11, 4, 8]. Thrombosis may extend and become the source of fatal pulmonary embolism, an adequate anticoagulant therapy. The thrombosis thrombophlebitis usually subsides after removal of the malignant lesion [12]. The thrombosed veins are variable. Some authors have described the change thrombophlebitis, while other considers it to be phlebo thrombosis.

Thrombophlebitis may be associated with sign of inflammation, pain tenderness, rise in temperature and marked edema. When arteriolar spasm occurs [8] the picture of phlegmesia albadolens may develop and require amputation. In other cases thrombi can be removed from the open veins without any sign of inflammation. Detailed micoscopical findings are not reported in the literature.

Causes and Comments

Explanation of the relation between cancer and thrombophlebitis can be approached under two headings:

I. The first theory suggests that thrombosis occurs because a factor is produced by the tumor which induces clotting.

II. Discovery of an association of pancreatic carcinoma with thrombosis led many authors to postulate an increase in pancreatic enzymes released into the circulation.

Lipase was incriminated because of its effect upon cephalin, augmented absorption of Vitamin K [3], or a secondary alteration of liver function. Trypsin was suspected as a cause because of its action on fibrinogen a thrombin like action [13].

It's difficult to increase tryptic activity in the peripheral blood due to the presence of an antitryptic substance [3] which is usually increased in carcinoma and in other cachexia producing diseases [14].

Oelgoetz and associates were unable to increase enzyme levels in the blood of normal animals and postulated that excess enzymes were stored in the liver and spleen. The frequency with which thrombosis occurs with cancer of the body and tail of the pancreas a s compared with the cancer of the head of the gland has led some authors to suggest a change in pancreatic structure and function in case of cancer of the head, secondary to occlusion of the pancreatic duct.

Huguenin [15] and his associates demonstrated a greater decrease of lipase than trypsin in duodenal juice following secretin injection when the head of the pancreas was involved. Meersseman and his co-workers arrived at different conclusion. The volume of pancreatic juice was reduced but its enzyme content matched the normal individual. It seems probable that cancer of the head, by obstructing the bile and pancreatic ducts and decreasing proteolytic enzymes released into the duodenum, produce secondary change in the liver parenchyma, obstructive jaundice and biliary cirrhosis. Also, proteolytic enzymes are essential for protein digestion and release of methionine that provide the methyl group for choline synthesis which has a lipotropic action that prevent fatty degeneration and Laennec's cirrhosis, which will counteract any tendency for increased coagulation due to decreased prothrombin and fibrinogen concentration [16, 17].

Sproul [3] found that in three cases of cancer of the head with thrombosis two of them did not have ductal obstruction. Some authors failed to demonstrate a relation between the histological structure of the tumor and thrombosis to support the proposition of Lafflc [18], that a glandular carcinoma may secrete some substance responsible for clot formation.

The second group of theories describes a hyper coagulable state due to either secretion of a foreign substance by the tumor, or release of thromboplastin [11] as a result of tissue damage. Amundsen and his co-workers [19], in a study of a hype r coagulable state in patients with extensive or metastatic malignant disease , found accelerated generation of thromboplastin due to an increase in a substance indistinguishable from factor VIII. Waterburg and Hampton [20] found a normal antihemophilic factor, however, there was an increase in factor IX, and they incriminated this as a cause of the hypercoagulable state.

Levin and Conley [21] attributed thrombosis to an increase in the number of platelets, while Moolton and Adelsrn [22] attributed the hyper coagulable state to increased adhesiveness of platelets. Riggenbach and Von Kaulla [23] investigated urokinase excretion in 25 patients with carcinoma in an attempt to explore the hypercoagulable state on a basis of decrease activity of plasmin system. They found that patients with the poorest prognosis had the lowest urokinase excretion, those who received surgical cure excreted normal quantities of urokinaze. Plasmin system in the normal condition is balanced by the clotting factors and both together are responsible for the fluidity of the blood. An unbalance between the two systems will lead to a fibrino genemia on the one hand and intravascular clotting on the other hand.

Mider, Alling and Morton [24, 25] studied the plasma protein pattern of 222 patients with malignancy using electrophoresis. They found an increase in globulin and fibrinogen with decreased albumin. Krost and Kratochvil [8] found a cryoprotein which has the character of fibrinogen in a patient with cancer. They called it cryofibrinogen and postulated that it may be a transient product in the conversion of fibrinogen to fibrin. Others, including Lowe [26] have not confirmed the presence of an abnormal protein in the normal tissue from which the tumor has, raised [23, 27].

They are generally responsible for tumor rejection transplant to an allergenic host. These antigens were investigated thoroughly in mice [28] and were found to be controlled by genes, present in various locations at different chromosomes.

H2 locus was described by Grorer [29, 30] and has shown to control antigens capable of affecting prompt rejection of grafts carried across this histocompatibility barrier. Thirteen of such loci have 'been described in mice [31-34]. Further studies were carried to investigate the presence of these antigens in animal and in man [35].

Second types of antigens common to both normal and malignant tissue are organs or specific antigens. These antigens may be lost during ontogenesis [36].

Abelve [37] described a third type of antigens in malignant tissue. These antigens are abs cent from normal tissue but present during the embryonic life of the anima of the animal Recapitulation of these antigens result of antigenic reversion.

A search for tumor specific antigens were made and were more easy to demonstrate that some tumors loose tissue specific antigens during ontogenesis Chemical carcinogens were found to attach themselves to neighboring unaffected tissue but not to the cells of the tumor they have induced [23] loss of this carcinogen binding protein which may 'be a "self-marker " recognized by the neighboring tissue may be responsible for invasion of this tissue by the malignant cells [38].

By complement fixation test Weiler [12, 39] was able to demonstrate loss of organ specific antigens in the hamster kidney. Narin et al., by using fluorescent antibody technique demonstrated loss of antigens in rat liver G.I. and skin tumor of man, this loss of tissue specific antigens may be a possible factor leading to breakdown of methods of intercellular control.

It was found that auto-antibodies in patients with Hashimoto's disease were able to react with normal thyroid tissue but not with malignant thyroid [40] which provides a clinical evidence for the absence of antigens present in normal thyroid but not in thyroid tumor. On the other hand tumors induced by hydrocarbons and virus may acquire new antigens. Gross [41] was the first to use the pure line strain of mice to demonstrate the presence of tumor specific antigens of methyl cholanthrene induced tumors.

Out of 115 mice of C3 H strain inoculated with the tumor he noticed temporary growth and then regression and disappearance of the subcutaneous nodule in 21. When they rechallenged with the same tumor the animals showed a high degree of resistance as compared to the control. Such acquired resistance was found to be specific, when two of the females in the resistant group developed spontaneous mammary carcinoma. These animals were still found to be resistant to M.C. induced tumor while their mammary carcinoma grew steadily.

Foley [42] reached the same results. Prehn and Main [43] transplanted M. C. induced tumors to syngeneic mice and after the tumor formed a palpable nodule it was removed surgically. When these mice were rechallenged with the same tumor they were found to be more resistant than the control. Normal tissue derived from the same donor did not immunize against sarcoma, and mice resistant to the tumor challenge did not reject skin grafts derived from the same mouse in which the tumor had originated. They concluded that M.C.A. induced sarcomas have T.S.A. and that they are individually distinct for each neoplasm.

Old, Boyse, Clark and Carswell [44] obtained the same results with M.C.A. and dibenzenthracence. Tumors of known viral etiology behave differently so far that they possess T.S.A. which are common to all neoplasms induced by the same virus and different from those produced by other viruses [9]. Polyoma virus-induced mouse tumors were the first neoplasms of viral etiology in which T.S.A. were detected.

Injection of polyoma virus into immature mouse resulted in the formation of polyoma tumor [45]. Immunologically mature animals do not develop tumors when infected with the polyoma virus but instead develop antiviral antibodies.

Following infection with polyoma virus both newborn and adult mice can be shown to be resistant to tumor isograft of polyoma origin [46]. Lymphocytes from virus infected adults are effective in inhibiting tumor growth when mixed with polyoma tumor and inoculated into susceptible hosts Sjorgen emphasized that the virus induced new antigens in infected cells and that antiviral antibodies are not prerequisite for resistance [9, 47].

Burnet [48, 49] has postulated that hemograft immunity is essentially a hemostatic mechanism which is a by-product of what he called "cell surveillance" which is necessary to recognize and destroy any cells that undergo spontaneous mutation as a result of error in nucleotide replication during cell mitosis. Burnet's view that the immunological mechanism is important to protect. The organism against neoplasia was supported by many experimental works. Neonatal thymomectomy which decreases cellular immunity [50] make experimental animal more sensitive to onchogenesis, that even the room infection with polyoma virus can produce neoplasm [46].

Certain virus induced tumor can undergo spontaneous regression which can be abrogated by whole body x -irradiation or by cytotoxic drugs [35]. Patients with immunological deficiencies are prone to develop neoplasms particularly of the lymphoreticular system [51]. Rejection of hemografts of malignant cells in patients with advanced cancer is delayed, sometimes indefinitely. And, one patient with advanced cancer who received a homo transplant of another tumor, the latter metastasized to the regional lymph nodes [23], which were not due to general debility, as in patients with debilitating non-neoplastic disease.

The rejection of hemograft of malignant cells is the same as in normal control [52]. Scanlon [53] took a small piece of a melanoma from a 50 year old woman and transplanted it to her 80 year old mother who subsequently died from wide spread metastases from this tumor. The fact that the recipient was old and Mantoux test was negative raises the possibility that there may have been some impairment of her immune mechanism.

Wilson [54] transplanted a cadaveric kidney from a donor who died from bronchial carcinoma and 18 months later the tumor was found surrounding the transplanted kidney which is morphologically identical with that of the donor's. Immunosuppressive treatment was stopped and the kidney underwent rejection and was removed. The tumor then regressed and an exploratory laparotomy six months later failed to show any trace of the tumor.

Tumor Specific Antigens in Human Carcinoma

Klein [55-57] found that Burkitt's lymphoma cell from fresh biopsies, and from lines propagated in culture possess antigens which could be detected [58] by inoculation of tumor cells with serum from Burkitt's patients. He obtained the strongest reaction from patients whose disease was in remission and that 1-rho responded well to chemotherapy. This finding suggested that the antibodies detected were involved in the host's defense against Burkitt's lymphoma [56].

A special case is that of chorio carcinoma of the female which as would be expected contains antigens from the husband. Patients with choriocarcinoma have been found to accept skin grafts from their husbands [58]. A case reported by Cinader [59] of a patient with metastasizing chorio carcinoma and who failed to respond to chemotherapy. The patient responded very well to recurrent injections of extract of leucocytes and sperms from her husband with complete remissions of the disease over a seven month period.

Antibodies Involved in Cancer Immunity

Antibodies formed against malignant disease are both of humoral and cellular type. It was found that the prognosis of carcinoma of the stomach and breast are related to the degree of nuclear differentiation, amount of lymphoid infiltration in the tumor and the presence of sinus histocytosis in the regional lymph nodes [60-62]. The greater the degree of differentiation, lymphoid infiltration and sinus histocytosis the better the prognosis. A similar situation arises in Hodgkin's disease, lymphocytic depletion is associated with poor prognosis and widespread disease, lymphocytic or histocytic proliferation is associated with better prognosis and localized disease. It was found that patients with malignant disease have lymphoid cell pattern in the peripheral blood which is identical with autoimmune disease. There was an increase of both large and medium lymphocytes actively synthesizing D.N.A, as well as increase in the plasma cells [63].

Brunschwig in 1965 [64] Southam in 1964, 1966 and 1967 [65-67] studied the cellular antibodies by using the neutralization test. They inoculated a mixture of patient's lymphocytes and tumor cells subcutaneously to the patient. They reached a conclusion that patient's lymphocytes have some inhibitory effect upon the growth of the transplanted tumor cells whereas lymphocytes from a healthy donor have no effect. Hellstrom in 1968 [68, 69] found that lymphocytes of the neuroblastoma in patients inhibited colony formation by the neuroblastoma cell in tissue culture.

Humoral Antibodies

In leukemia of viral etiology humoral antibodies were demonstrated against the neo antigen [70]. Klein et al. [71, 72] found that two types of antibodies are present in the serum of patient with African lymphoma. One against the EB virus the other was directed against the antigen present in the cell membrane Lewis [73] has shown that some patients with 1ong history of malignant melanoma has antibodies in their serum which is cytotoxic to the malignant cell but not to other melanoma cells.

Evidence from Delayed Type Hypersensitivity:

Brent et al., [74] showed that evidence of hemograft immunity might be indicated by the presence of delayed skin hypersensitivity reaction to a microsomal preparation of donor tissue. Hughes and his colleagues [19, 23] showed that 25% of patients with malignant disease gave evidence of delayed hypersensitivity type against the microsomal fraction of their own cancer tissue, while control preparation from normal tissue gave no response.

If we consider that tumors contain tumor specific antigens which are distinct from the histocompatibility antigens of the normal tissue, then we must consider why the host does not show evidence of effective immune reaction against his own tumor. This can be explained by the following immunological phenomena:

Enhancement: Immunological enhancement may offer an explanation by which tumors can be protected in vitro from the cytotoxic effect of immune cells. The term was introduced to denote a phenomenon in which humoral antibodies were found to facilitate the growth of the transplanted H2 incompatible mouse tumors [7, 75, 76].

Billingham et al., [77] distinguished between afferent, central and efferent forms of enhancement; afferent enhancement occurs if serum antibodies bind to antigen released from grafted cells and therapy weaken the antigenic stimulus. In the central type the antibodies directly repress the immunocyte's efferent type is defined as a protective coating of tumor cells with humoral antibodies which bind to the tumor specific antigens and protect the cell from the cytotoxic immune response.

Antibodie's mediating the efferent response must be nontoxic or less toxic than the cytotoxic immune response which they counteract [78, 79]. It is possible that a nontoxic antibody may also protect a cell from destruction by a cytotoxic complement fixing antibody by competition with the same antigenic receptors [80]. 7 - S antibody was found to have great avidity for surface antigens [81, 82] and less toxic than 19-S gamma globulin [83]. 7-S gamma globulin was separated into two fragments electrophoretically. 7-Sl is non-complement fixing [84] and may interfere with the attachment of 7-S2 antibody which is complement fixing and may be cytotoxic in vivo.

Brunner et al. [85], have demonstrated that cultures of tumor cells are not killed by immune H2 incompatible lymph node cell if they have been previously inoculated with serum directed against their H antigens that are foreign to the L.N.C. Bubenick and Koldovsky [86, 87] have demonstrated that M.C.A. induced mouse sarcoma grow better in mice which had been inoculated with serum from syngeneic donors immunized with M.C.A. tumors.

Specific Immunological Tolerance:

Immunological tolerance as originally described by Medawar refer's to a state of immunological un-responsiveness induced in fetal or early adult life by contact with antigenic material. Billingham et al. [81, 88] showed that if fetal mouse from C.B.A strain is inoculated in utero with a suspension from an adult mouse of another strain, "Strain A". Then when it grows up, the C. B.A. mouse will be found to be partly or completely tolerant of the grafts transplanted from any mouse belonging to the strain of the original donor. This phenomenon is the exact inverse of actively acquired immunity which may develop if exposure to the cells of the potential donor was delayed until after birth, they described it as active acquired tolerance. The induction of tolerance was found to be governed by not only the animal but by the dose and nature of the antigen employed [45, 89-91].

One way of inducing tolerance in adults is by administration of large doses of antigen which are not too distantly related to the host. New born mice artificially infected with polyoma virus became tolerant and developed tumor in later life while if infection occurs in adult life immunity develops and no tumor appears.

Feldman and Machtigal [92] postulated that the host may be partially tolerant to his autoclotonus tumor which may be due to the antigenic load provided by the rapidly growing tumor. Also the anti-genic difference between the host and its tumor may be slight which makes the host more amenable to the establishment of tolerance [91].

Suppression of the immunological reactivity can be produced by the tumor and by the carcinogenic agent [53]. Graham [93] described a tolerance factor present in certain human cancer tissue and was found to prolong the survival time of mouse homologous grafts. Hellstrom EK and Hellstrom I [94] presented the following evidences of:

Similarity between allograft reaction and the rejection of tumor syngrafts

1. Rejection of tumor syngrafts is specific; mice immunized against unrelated tumors are as sensitive as untreated control.
2. Animals can be immunized against allografts and tumour syngrafts and consequently reject the tissue containing the respective antigens by the second set reactions.
3. Whole body irradiation with 3500-5000 suppress primary allograft reaction [2] and host resistance to tumor syngraft as well [36] with little effect on second set reactions to both kinds of grafts [2, 95, 96].
4. Thymemectomy at birth decreases both the allograft reaction [97] and host resistance against tumor specific antigens [46].
5. Both types of reactions can be suppressed by treatment of the animal with antilymphocyte sera [39, 98].

6. Allograft reactions and immune reactions against tumor syngrafts can be passively transferred with lymphocytes but generally not with sera.
7. Histological preparation from the site of reactions of either allograft [99] or tumor syngraft [36] shows a heavy infiltration with lymphocytes plasma 1 cells and macrophages.

The Mechanism of Allograft Rejection

That the lymphocytes are the cells which are important in immunity against both allograft and tumor specific antigen was demonstrated both by tissue culture experiment [54, 100] and neutralization test in Vivo [58, 101, 102]. Granger and Weiser [103] were able to demonstrate that macrophages from animals that were immune to certain isoantigens destroy target cells that carry these antigens. Adherence of the immune cell to the target cells was found necessary for their cytopathic effect [45]. If such adherence is interfered with by incubation of either lymphocytes or target cells with specific humoral antibodies destruction of the target cell will be abrogate.

Humeral antibodies were found to be essential for the attachment of the immunocytes [45]. The cytophilic antibodies, are produced by lymphocytes and plasma cells, were found to be taken by macrophages [47] and essential for their cytopathic effect. Humoral antibodies are engaged in allograft immunity in a more complicated way than the cellular type. Antibodies which are non-competent fixing can interfere with the attachment of the immunocytes "Enhancement". Some antibodies are cytotoxic and complement fixing have a synergistic effect. In addition it seems that the humoral antibodies are the type involved in thrombosis which represents an essential feature of graft rejection. It can be produced by different mechanisms. Antibodies react with antigens fix complement which has an important chemotactic influence on the migration of leucocytes.

The trimolecular complex of 5, 6, and 7 was recently found to be the chemotactic factor of the complement [104]. P.M.N. are essential for the generalized and localized Schwartzman reaction and for the vascular damage which was originally demonstrated in Arthus phenomenon. Animals treated with nitrogen mustard or heterologous anti-P.M.N. Sera has shown a striking inhibition of the reaction [3, 66, 105 - 108].

Kenneth et al. [109] studied the mechanism of hyper acute renal rejection in sensitized canine recipient, in one of their experiments. A systemic clotting disorder developed which cannot be distinguished from disseminated intravascular coagulation. Another graft studied by serial biopsies showed early disposition accompanied by rapid removal of fibrin which suggests that both the coagulation and fibrinolytic system are activated.

William et al. [110, 111] studied seven cases of renal transplants in men. Biopsies taken one hour after the anastomosis however the accumulation of P.M.N. leucocytes in Glomerular & Peritubular Vessels, in one case, this was observed to be followed by progressive thrombosis and accumulation of fibrin followed by extensive cortical necrosis.

The significance of hyper acute rejection in cases received multiple grafts pointed to its immunological basis. And the absence of mononuclear cell infiltration from the graft suggests that the humeral antibodies are the type involved in this type of rejection. That the P.M.N. accumulation is the first essential step in thrombosis and fibrin deposition in transplanted renal allografts in goats passively immunized against the renal antigens. They found accumulation of P.M.N. to be followed by thrombosis, fibrin deposition, and cortical necrosis of the transplanted kidneys.

Kissmeyer-NieJsen et al. [112] stressed the similarity between the late changes of graft rejection and Schwartzman reaction. In addition antigen antibody reaction may be associated with vicious metamorphosis of the platelets, a morphological and biochemical change that accompanies the process of blood coagulation. Complement may be essential for the process [58, 113]. Vicious metamorphosis, A.T.P. consumption and contractile activity was found to occur in the presence of antigen antibody complexes in spite of the presence of hirudin which is a powerful inhibitor of thrombin which suggest that primary activation of the clotting system does not seem to be necessary [102]. Also phospholipid liberated from platelets during viscous metamorphosis may activate the intrinsic factors of the clotting system [21, 114]. It was found that antigen added to the whole blood from immunized rabbit's in vitro result in prompt agglutination of leucocytes and platelets.

Robbins et al. [58] studied the effect of antigen antibody reaction on the clotting time of the experimental animal. They found that the addition of antigen to' the whole blood of immunized animal in vitro result in marked reduction of the clotting time as compared to the control. That the humeral antibodies are the type involved was proved by the addition of antigen with small amount of serum from an immunized animal to a whole blood from a normal animal. A rapid coagulation of the blood was noticed. They postulated that the acceleration of the clotting time may be related to platelet clumping since the coagulation time of the plasma was not affected.

Arteriolar spasm, damage and thrombosis may play an important role in graft rejection in the experimental animal arthus vasculities [67, 106]. The vascular lesion seen in serum sickness [115], were found to be produced by P .M.N. immigration. And the precipitating types of antibodies are the usual type involved.

Hollenverg N.K. [75] studied the blood flow in allograft renal transplants. Biopsies were taken at the same time. The early damage was noticed in the capillaries and venules but it was the arterial injury which was important in the rejection phenomenon. Arterial spasm plays an important role in the process of rejection, as evidenced increased sensitivity of the blood vessel s to vasoconstrictors during the rejection phenomenon.

Thrombosis of malignancy is usually associated with slowly growing tumors. This can be explained. Either by the fact that such tumors present to the lympho reticular system of the host an antigenic stimulus which is not too great to cause immunological paralysis. On the other hand antibody response may be favored. The tumor may happen to grow in an immunologically competent host. In both cases antibodies formed will react with tumor specific antigen and will induce thrombosis. Antibody responses may be enhanced also if the tumor specific antigens are different from the histocompatibility antigens of the normal tissue. In addition the chemotactic factor of the compliment fixed by the antigen antibody complexes may explain some of the hematological changes that are associated with malignancy and not accompanied by bone marrow replacement.

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