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Transplantation of Marrow and Whole Organs: Experiences and Comments

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IN 1949 Jacobson[1] demonstrated that mice exposed to lethal general radiation did not die if their spleens were shielded during their radiation exposures. Shortly thereafter Lorenz and colleagues[2] showed that animals exposed to lethal doses recovered if given an intravenous injection of fresh bone marrow cells. About 1955, several lines of evidence proved that these recoveries were due to a repopulation of the bone marrow spaces by the marrow cells that had been infused.[3-6] It was found that the heavy radiation exposure had weakened the immunologic defences that ordinarily cause rejection of transplanted tissue when donor and host are of different genetic origin. The infusion of foreign marrow was thus able to repopulate the marrow spaces of the irradiated recipients. These discoveries opened exciting possibilities in the field of transplantation, in the use of marrow for the treatment of radiation casualties or for the aplasias due to disease, therapeutic radiation or chemotherapeutic agents.[7, 8]

This report describes studies on marrow transplantation that illustrate some of the successes, some of the failures, and some of the problems in this field today as met in our efforts with man and dog.

Studies in Dogs

For our dogs, 600 r of whole-body irradiation is an LD_{100} dose. Fig. 1 illustrates the white blood cell counts in a group of dogs given 600 to 1200 r of whole-body irradiation followed by an infusion of a sample of the dog's own bone marrow that had been removed prior to radiation exposure.[9] Note that the white blood cell count falls precipitously, reaching a nadir at five to six days. In dogs not receiving bone marrow, the leukocyte count never comes up again, and death usually occurs in 10 to 12 days. However, in this group of dogs that received marrow, there was a rapid return of the white blood cell count to normal. Fig. 2 shows the platelet counts in the same group. The nadir was reached in eight or nine days and was followed by return to normal values. In these dogs given autologous (isogeneic) bone marrow, there is of course no genetic incompatibility, no transplantation barrier. The marrow graft is rapidly effective, and the dogs remain in apparent good health throughout the procedure. Fig. 3 is a picture of this group of dogs taken approximately one year after irradiation. Except for some greying of the hair, they appear to be entirely normal. The group is still being observed, now three years after exposure, and so far no untoward late effect of irradiation has been observed.

If the lethally irradiated dog receives homologous (allogeneic) marrow, problems arise associated with the histo-incompatibility of donor and host. Death may occur for several reasons. The graft may fail to "take", it may "take" and be rejected, or it may "take" successfully and the animal may later die from a secondary syndrome or "homologous disease" that is presumed to be a graft versus host reaction.[10, 11] The following examples are illustrative.

Fig. 4 presents hematologic data in a dog receiving 1565 r of whole-body irradiation followed by 2.8 billion homologous marrow cells. The white blood cell count fell rapidly, then rose to values of 2500 white blood cells per c.mm. by the 8th day. There was a subsequent decline in the white blood cell count to values of less than 100 cells per c.mm., with death on the 15th day. This pattern

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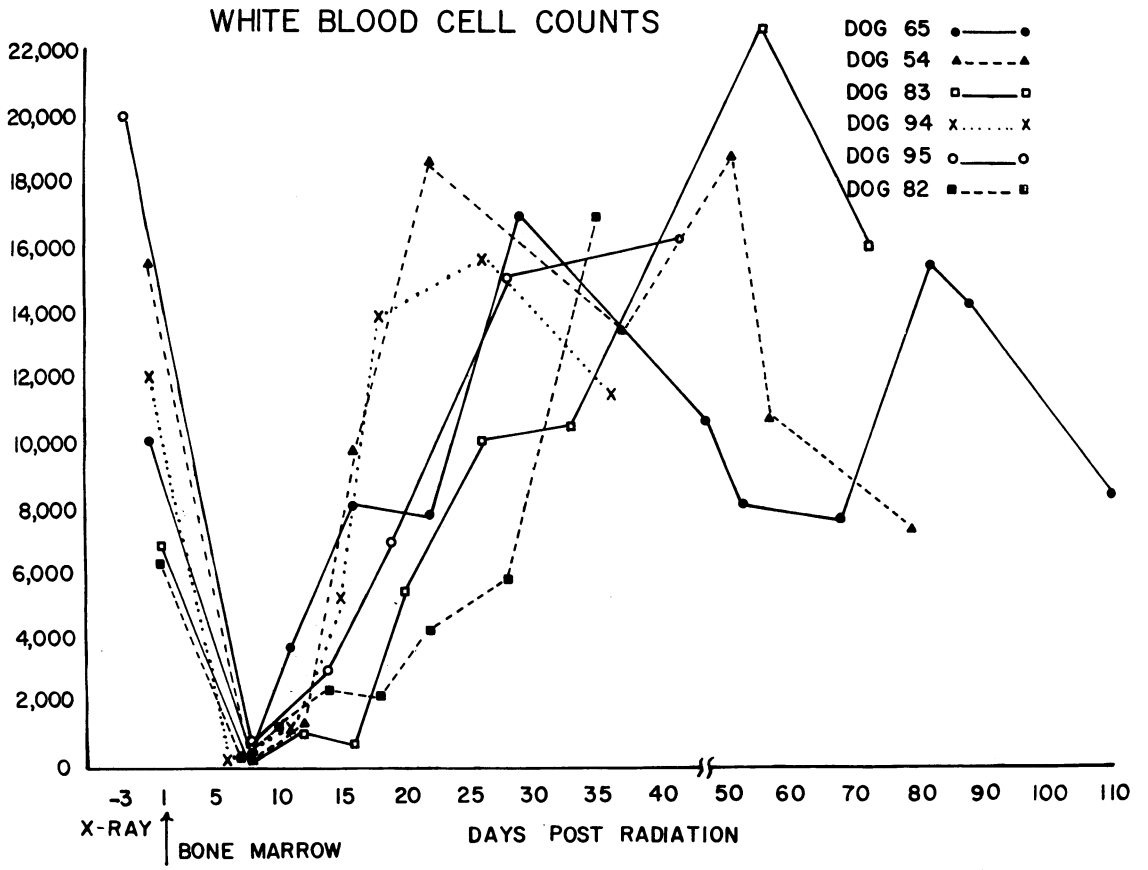

Fig. 1.—Peripheral white blood cell counts on six dogs that received 600 to 1200 r of whole-body irradiation followed by autologous marrow infusion, (*Blood*, 15: 258, 1960.)

is interpreted as an early graft of the marrow followed by rejection.

Fig. 5 shows the hematologic events in a dog given 1530 r of whole-body irradiation and, on the next day, an infusion of 16 billion homologous marrow cells from an unrelated donor. Note the abrupt fall in white blood cell count and platelet count and the rapid recovery that is evident by about the 6th day. In this male recipient the appearance of female leukocytes from the female

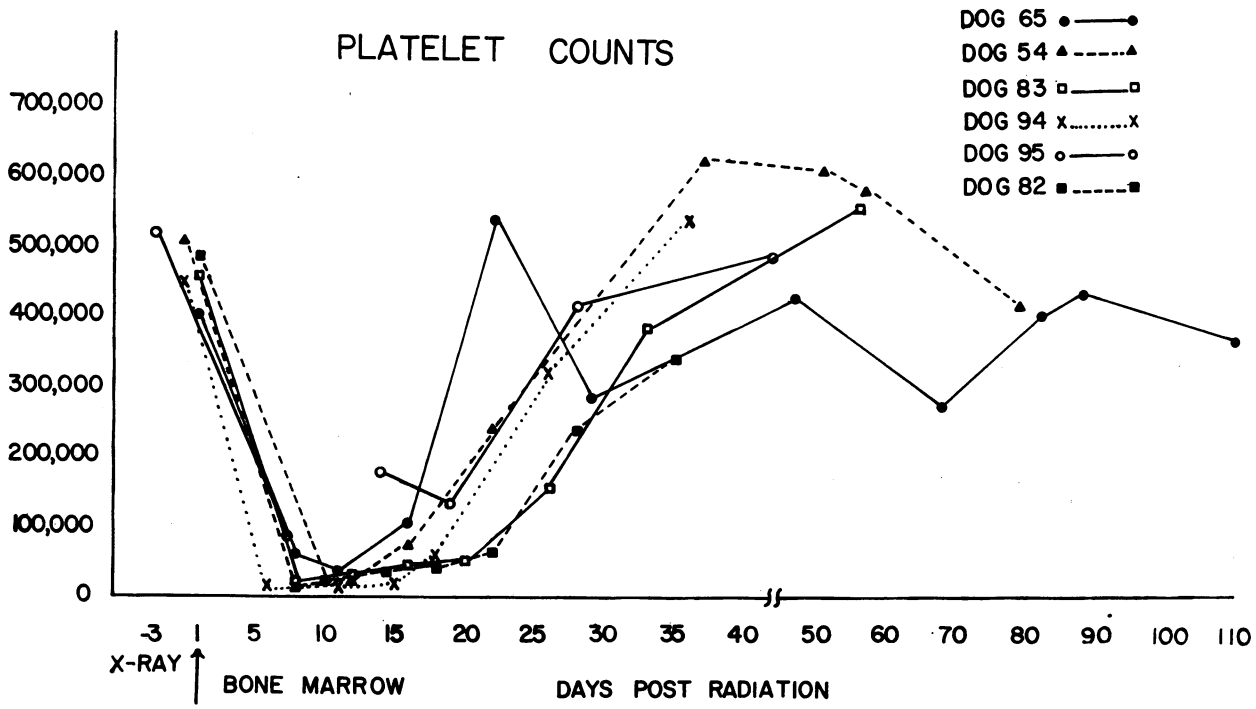

Fig. 2.—Serial platelet counts on the same six dogs shown in Fig. 1. (*Blood*, 15: 258, 1960.)

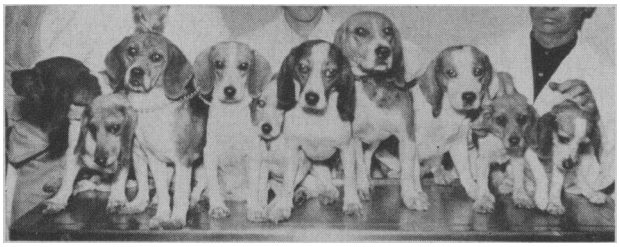

Fig. 3.—A group of dogs that received supralethal whole-body irradiation followed by autologous marrow infusion some months previously. Greying of the hair is the only late radiation effect observed.

donor constitutes proof of a successful marrow graft. However, despite the rapid hematologic recovery the dog died of pneumonia on the 21st day. The marrow graft had restored marrow function but not immunologic defence. Susceptibility to infection in the weeks post irradiation is a characteristic of animals that have received allogeneic grafts of marrow. It is correlated with a lack of cellularity in their lymph nodes, spleens and Peyer's patches. Presumably repopulation of these areas is retarded by a wasteful reaction of the foreign lymphocytic cells against their new and foreign home sites.

Fig. 6 depicts the events in a dog given 1565 r of whole-body irradiation followed by 17 billion marrow cells. There was the usual rapid decline in white blood cell count, with a very rapid recovery and a return to normal hematologic values except for a low lymphocyte count. This dog appeared to be in good health for the first two months post irradiation. Subsequently he began to lose weight, and eventually he died on the 116th day, of malnutrition and infection. Late deaths of this type with malnutrition as a prominent feature are typical of the secondary syndromes observed in animals with successful grafts of marrow. They too presumably represent a reaction of immunologically effective lymphocytic cells against their defenceless hosts, a graft versus host reaction.[12]

Despite these various complications associated with grafts of allogeneic marrow, some dogs do live through the period of secondary syndromes and recover completely.[11, 13] Such animals show a slow repopulation of their lymph nodes and an eventual recovery of their ability to make antibodies, as for example against distemper. The duration and the severity of the period of their secondary syndromes are presumably determined by the degree of histo-compatibility that fortuitously occurs between them and their donors. In an outbred population this degree of compatibility is difficult to predict for any given pair, but its importance in determining the incidence of recovery and long-term survival is clearly shown by studies of transplantations between inbred strains of mice having varying degrees of similarities in their H-2 or histocompatibility genes.

Once they have survived the period of graft versus host reactions, the dogs appear to be in good health except for greying of the hair. Fig. 7

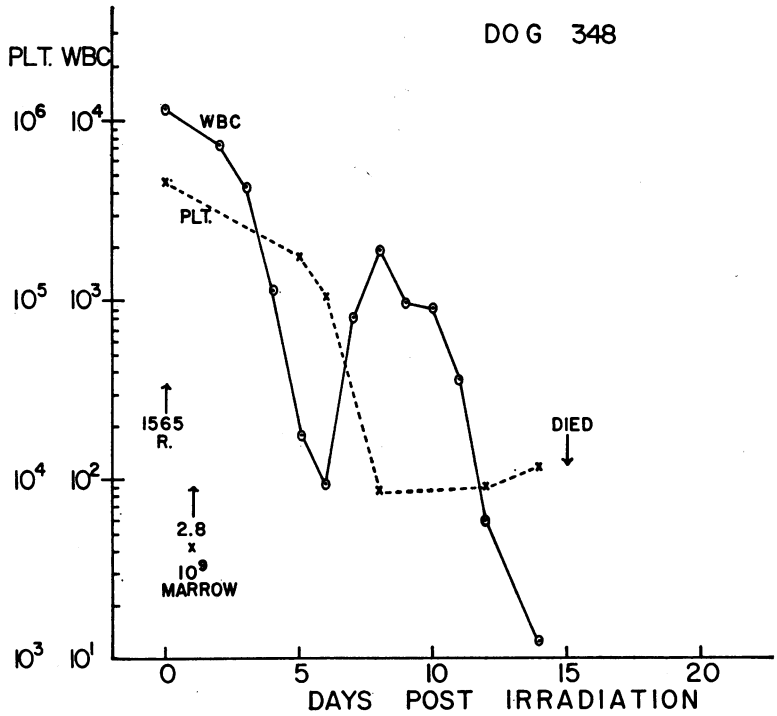

Fig. 4.—Hematologic data in a dog that received 1565 r followed by 2.8 x 10^9 homologous marrow cells. The leukocyte pattern is interpreted as an early "take" followed by a rejection of the marrow graft.

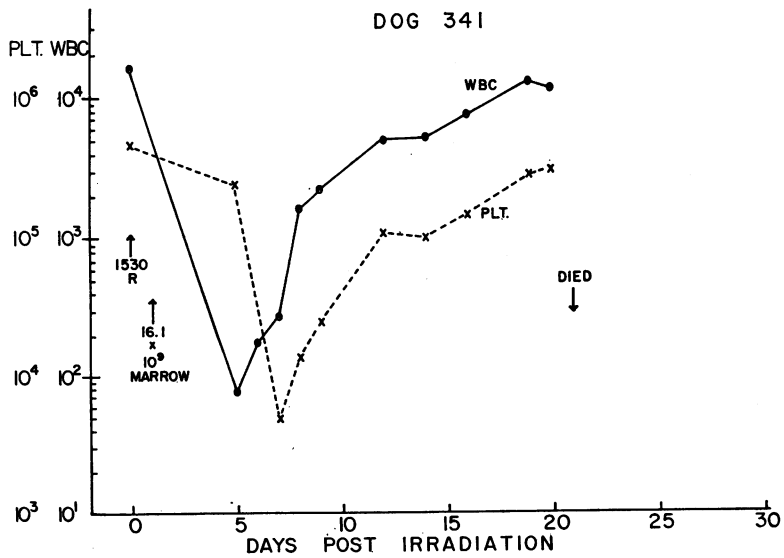

Fig. 5.—White blood cell and platelet counts in a dog that received 1530 r followed in one day by 16.1 x 10^9 homologous marrow cells. Despite prompt hematologic recovery the dog died on the 21st day, of pneumonia. (*Blood*, in press.)

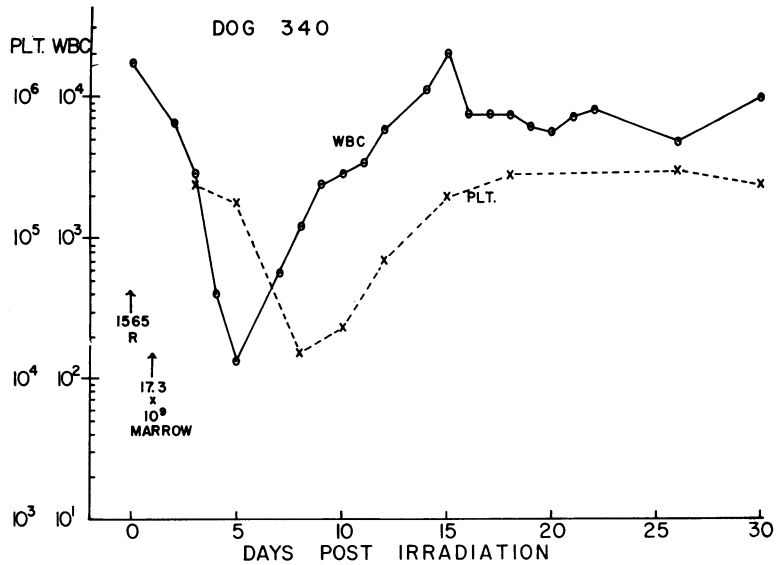

Fig. 6.—White blood cell count and platelet count in an irradiated dog with a marrow graft. The dog died after 116 days of "secondary syndromes", presumed to be graft versus host reactions, characterized by weight loss and terminal infection. (*Blood*, in press.)

is a picture of four of these long-term chimeras, including, in the background, two of their female donors. They have demonstrated return of fertility after a period of 18 to 24 months.[14] The dog standing against the gate is the longest living chimera, now 2½ years post radiation. These male dogs still have circulating female leukocytes. They accept skin grafts from their female donor but not from other dogs. The donors do not accept skin grafts from them.

Fig. 7.—The four male dogs in the foreground received 1800 r of whole-body irradiation 1½ to 2½ years ago. The irradiation was followed in each case by an infusion of marrow from an unrelated female donor. The marrow graft was successful and permanent. Two of the donors of marrow are shown in the background. These donors do not accept skin grafts from the dogs to whom they gave marrow. Their recipients of marrow accept skin from them but not skin from other dogs.

CLINICAL STUDIES

Let us turn now to some of the clinical observations associated with attempts to treat acute leukemia by whole-body irradiation and marrow transplantation. The patient with acute leukemia was selected as a suitable candidate for these studies because of the grave prognosis of this disease and because of the known radiosensitivity of the leukemic cell. All patients in this group had had conventional chemotherapy for leukemia and appeared to be in a terminal relapse at the time of whole-body irradiation.

Fig. 8 shows the hematologic data in one of the first of these patients.[15] This 16-year-old girl with acute leukemia in terminal relapse was given a midline tissue dose of approximately 325 r of whole-body irradiation. This irradiation was given from a 250 KV x-ray machine. Because of the small field, irradiation had to be given by quadrants. At that time we considered 325 r to be a large dose of whole-body irradiation. Nevertheless, the patient exhibited no sickness during or immediately after the irradiation. The white blood cell count initially was approximately 4500 per c.mm. with 20% polymorphonuclear leukocytes and 80% blast cells. After irradiation the white cell count fell to extremely low values. Reticulocytes disappeared and platelets declined to values of 10,000 per c.mm. After three weeks, evidence of returning marrow function was observed. There was a rise in the platelet and reticulocyte values. The increase in white blood cells was characterized by a normal percentage of polymorphonuclear leukocytes without the presence of blast cells. This patient had received an infusion of bone marrow from her sister on the day after radiation. After the return of marrow function, differential agglutination studies indicated that recovery was due to regeneration of the patient's own marrow without evidence of a successful marrow transplant. The patient was in complete remission for six months. She died at eight months, of recurrent leukemia. This patient shows that, contrary to conventional concepts, whole-body irradiation may produce a very gratifying remission in some patients with acute leukemia.

Late in 1958, a dual cobalt-60 unit (Fig. 9) was placed in operation at the Mary Imogene Bassett Hospital.[16] The cobalt source shown on the right is used for conventional teletherapy of malignancy. For whole-body irradiation studies, the collimating head is replaced by the wide-angle head. This cobalt source is then placed in opposition to the cobalt source on the left, the subject being placed in the narrow bed between the two

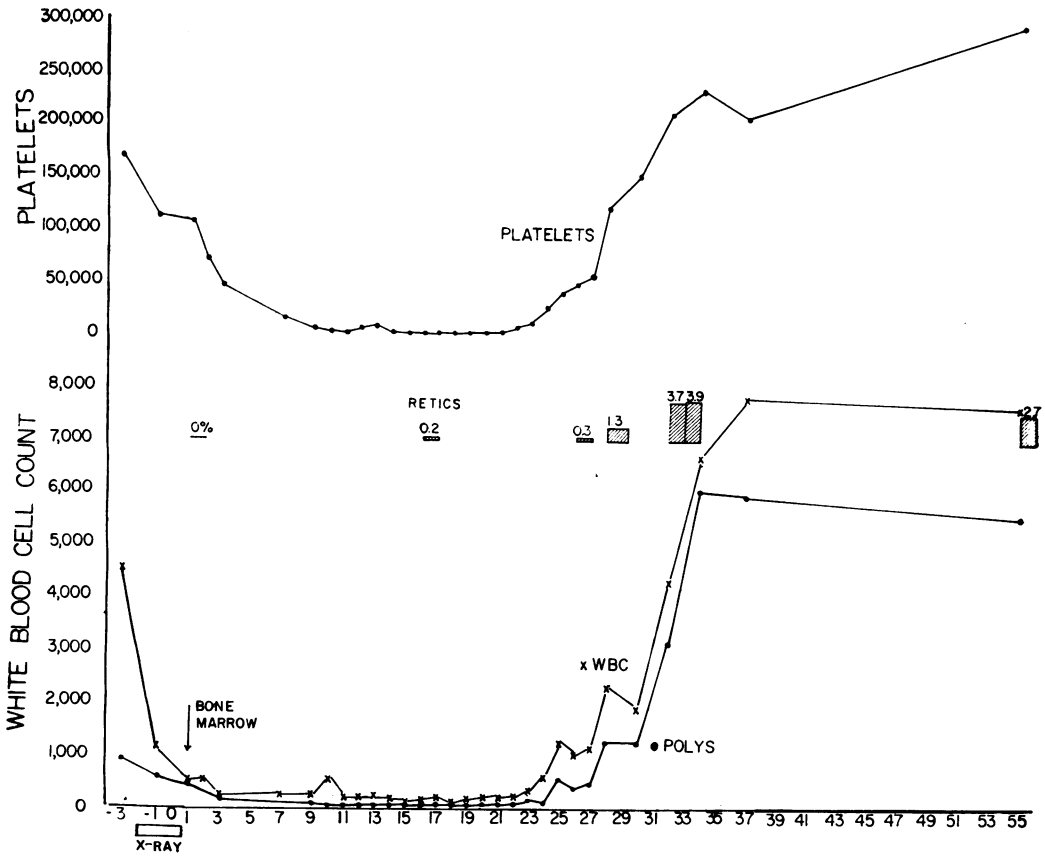

Fig. 8.—Summary of hematological observations in the case of a 16-year-old girl with acute leukemia who received 325 r of whole-body irradiation and a marrow infusion. Autogenous regeneration of her own marrow occurred beginning on the 23rd day. (*Blood*, 14: 1, 1959.)

sources. Each source is approximately 2½ metres from the patient. The resulting large field permits irradiation of the entire body at one time with much more uniform irradiation than had been previously possible. In the last three years all of our radiation studies in man and dog have been performed with this dual cobalt-60 unit.

Fig. 10 illustrates the hematologic events in the case of a 4-year-old girl with acute leukemia. This patient had a normal identical twin.[17] The patient was given 850 r of whole-body irradiation, followed by an infusion of marrow obtained from the normal identical twin. After irradiation there was the usual fall in white blood cell count and platelet count and a disappearance of reticulocytes. By about the 12th day, return of polymorphonuclear leukocytes to the circulating blood was observed. Subsequent recovery of the patient was uneventful except for a presumed viral gastroenteritis affecting both the patient and her mother about day 17. Fig. 11 shows some of the clinical events. There was fever in the second week post irradition, an observation common to most of our patients. Vomiting and diarrhea were mild. The patient lost most of her hair, but regrowth was well under way three months later. After 12 weeks, evidence of her leukemia recurred. There was a subsequent remission on administration of 6-mercaptopurine. Death from recurrent leukemia occurred 15 months after radiation.

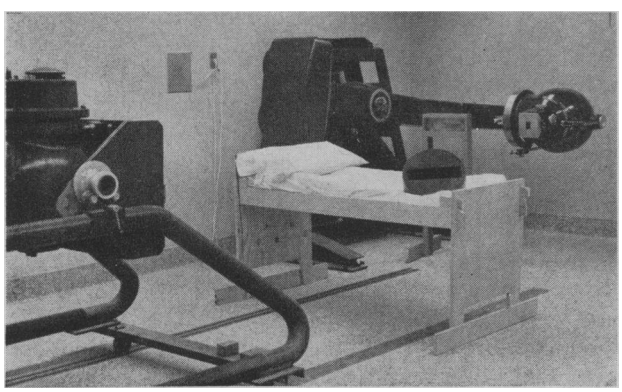

Fig. 9.—Whole-body irradiation room equipped with two opposed Co^{60} sources. (*Trans. Ass. Amer. Physicians*, 72: 284, 1959.)

Fig. 12 shows the hematologic data in a 26-year-old man with acute leukemia who received 1600 r of whole-body irradiation at a dose rate of 0.5 r per minute.[18] On the next day he received an infusion of isogeneic marrow from his brother, an identical twin. After the expected depression of circulating formed elements in the blood, recovery began on about the 12th post-irradiation day. On the 42nd day the patient was able to leave the hospital in apparent good health, as illustrated by the fact that he was able to drive his automobile 1000 miles in returning home. However, he suffered a recurrence of leukemia after two months, and died of

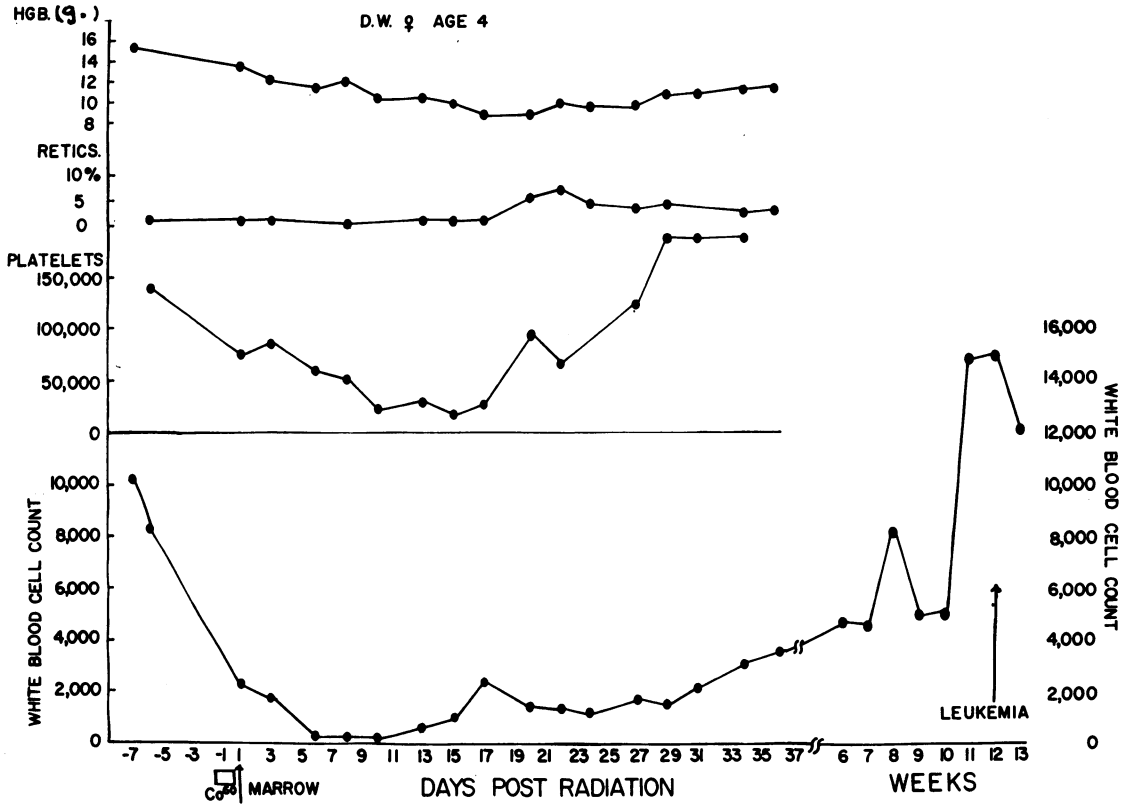

Fig. 10.—Hematological events in the case of a 4-year-old girl with acute leukemia who received whole-body irradiation followed by an infusion of marrow from her identical twin. The small rectangle labelled "Co^{60}" indicates the administration of a midline air dose of 850 r. The arrow on the abscissa indicates marrow infusion. (*J. Clin. Invest.*, 38: 1713, 1959.)

recurrent acute leukemia three months post irradiation.

Data concerning the 21 patients in our series have been summarized elsewhere.[19] The observations made in these cases lead to the following conclusion: (1) Patients can tolerate up to 2000 r of continuous whole-body irradiation at low dose rates without suffering unduly and without death from gastrointestinal causes. (2) A few hundred roentgens of whole-body irradiation does produce an appreciable remission in some patients with acute leukemia despite the fact that they have already had remissions on conventional chemotherapeutic agents and have become resistant. (3) Patients can be protected against the effects of large and presumably lethal doses of whole-body irradiation by the subsequent infusion of isogeneic bone marrow. (4) In the case of identical twins, despite the administration of marrow from an apparently normal twin, there is a discouraging early return of the leukemia. A similar observation has been made in two cases employing the patient's own bone marrow stored during a period of remission. It would appear therefore that whole-body irradiation followed by isogeneic marrow administration offers nothing more than a temporary remission to patients with acute leukemia. (5) Our attempts in patients to achieve successful transplants of homologous (allogeneic) marrow have in general

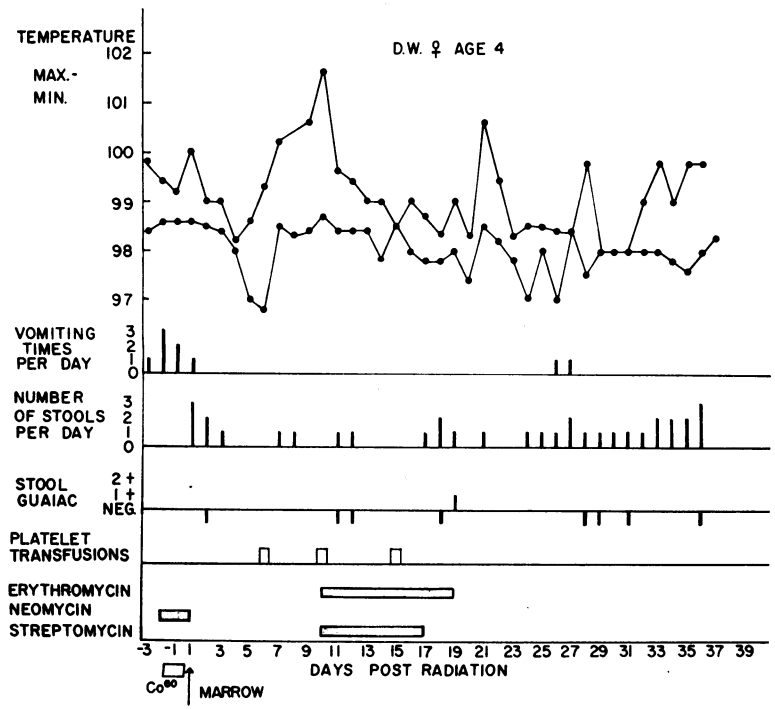

Fig. 11.—Clinical events in the case described in Fig. 10. (*J. Clin. Invest.*, 38: 1714, 1959.)

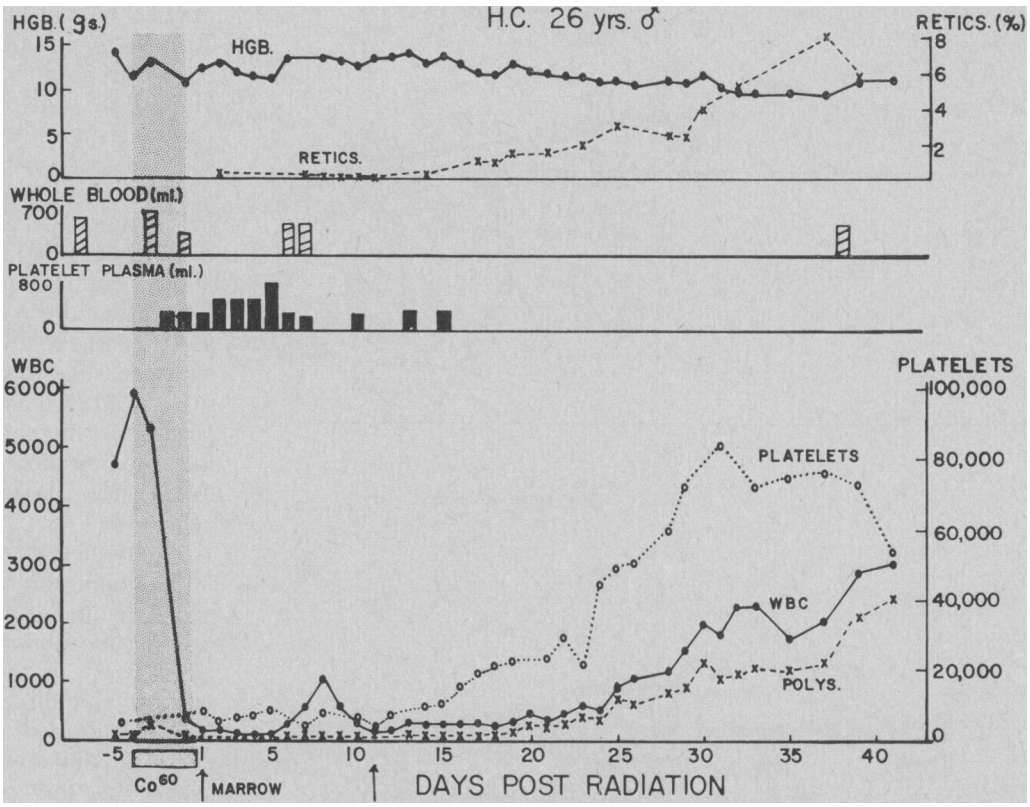

Fig. 12.—Hematological events in the case of a 26-year-old man who received whole-body irradiation followed by an infusion of marrow from his identical twin. The period of administration of 1608 r of whole-body irradiation is shown by the rectangle labelled "Co^{60}". (*Arch. Intern. Med.*, 107: 838, 1961.)

met with little success. One patient has had a transient graft of homologous marrow[20] and another patient had an apparently successful homologous graft but an early death from a staphylococcal septicemia. Mathé and his colleagues in Paris have also observed transient grafts of homologous marrow in man and may have observed death from secondary syndromes (graft versus host reactions) in two of their patients.[21] These observations indicate that allogeneic marrow grafts in man are difficult to achieve. Until such grafts have been achieved in man in some number, it is not possible to predict reliably the incidence, nature and severity of the secondary syndromes that may be expected in our species following the engraftment of foreign marrow.

CURRENT INVESTIGATIONS

From the observations just recounted it is apparent that isogeneic (autologous or isologous) bone marrow transplants work very well in man and in dogs, but that something more needs to be done to secure clinical satisfaction from grafts of foreign (allogeneic) marrow. Encouragement for further study has been derived from the fact that an occasional dog with an allogeneic marrow transplant survives for a long period in good health. Our present problem is to secure

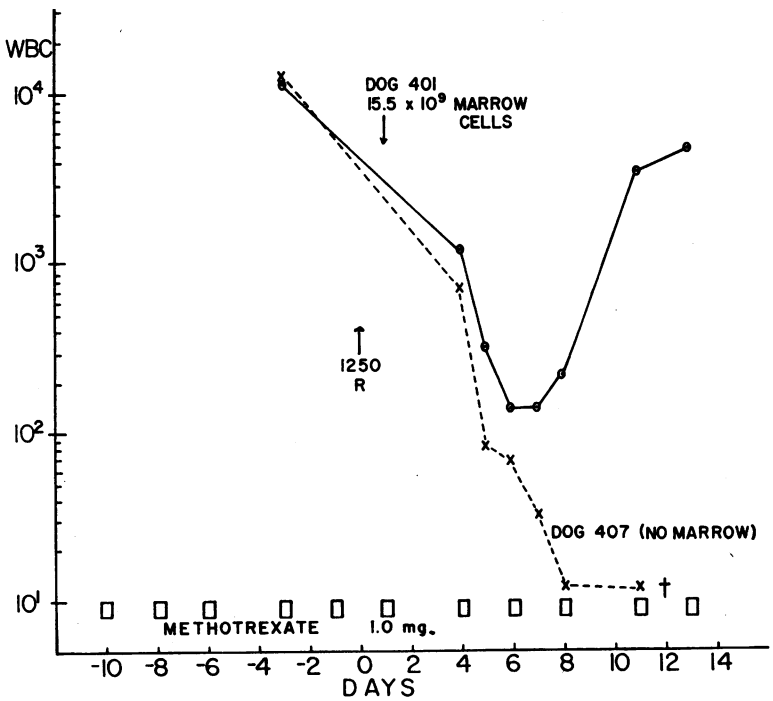

Fig. 13.—White blood cell counts and methotrexate administration in two dogs irradiated with 1250 r. Dog 401 received homologous marrow on the day after radiation and is alive and well 200 days later. Dog 407 received no marrow and died on the 12th day. (*Blood*, in press.)

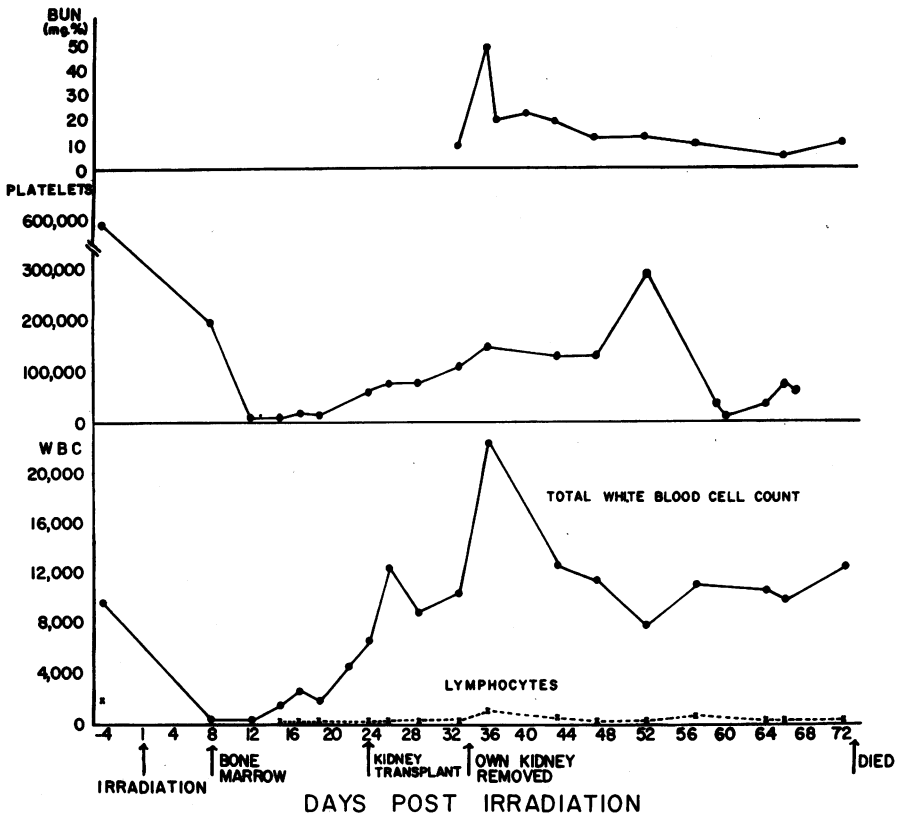

Fig. 14.—Data from a dog that received 1300 r of whole-body irradiation and a homologous marrow graft followed by a kidney transplant from the marrow donor. (*Surgery*, 46: 821, 1959.)

long-term chimeras of this type in dog and man with a reasonable degree of consistency. A number of laboratories are making efforts to accomplish this end along similar lines, particularly by the use of chemical agents to improve graft acceptance and to ameliorate the subsequent graft versus host reaction.

The antimetabolites methotrexate and 6-mercaptopurine interfere with immune mechanisms[22] and have been suggested as agents useful in prolonging homografts.[23, 24] In our laboratory we have been concerned primarily with the use of methotrexate as a supplement to supralethal whole-body irradiation and homologous marrow transplantation.[11] As an example of these studies, Fig. 13 shows the white blood cell count of two dogs that received methotrexate, 1 mg. three times a week beginning 10 days before an irradiation exposure of 1250 r. One dog received no marrow infusion after irradiation. He died on the 12th day. The other dog received 15.5 x 10^9 marrow cells on the day after irradiation. There was a rapid hematologic recovery, and methotrexate was stopped after 30 days. The dog is living and well 200 days later without having had a severe secondary syndrome. In a group of 11 such dogs there were four long-term survivors. Obviously, this leaves room for improvement, but the overall result is better than any we have previously obtained.

Attempts are also being made to induce tolerance in the adult animal by repeated exposure of the marrow donor to the tissue antigens of the prospective host and vice versa. The usual immune responses of donor and recipient are altered by concomitant exposure to a chemical agent such as methotrexate or by repeated sublethal doses of irradiation. The exposure to the antigens may be brought about by repeated cross-circulation between donor and recipient, by injection of large quantities of cells such as spleen cells, or by parabiosis. Some encouraging prolongation of homologous transplants has been achieved.[25]

The induction of tolerance in the immature animal by exposure to antigens of the prospective donor has been a subject of widespread interest and discussion. We have conducted no experiments in this area, and this aspect of the problem is mentioned only for completeness. We have, however, attempted to secure homografts of fetal hematopoietic tissue in dog and man but with a singular lack of success.[26, 27] One dog of 30 dogs studied had a transient marrow graft from fetal liver, but the graft was rejected after three weeks.

Homografts of Whole Organs

An irradiated recipient that has accepted a marrow graft acquires the immunologic environment of the donor and hence will accept a transplant of any other tissue of that donor.[28] For example, a few years ago in our laboratory Dr. John Mannick[29] administered 1300 r of whole-body irradiation to a male dog, and a few days later gave this dog bone marrow from an unrelated female dog. Fig. 14 presents the data on this recipient dog. On the 24th day post irradiation when there was evidence of successful marrow engraftment, a kidney from the marrow donor was transplanted to the recipient. Ten days later the dog's own kidneys were removed. The transplanted kidney then bore the whole load of nitrogen excretion quite successfully. The dog became ill on the 60th day post irradiation and died on the 73rd day. Autopsy demonstrated inclusion bodies characteristic of canine distemper. The marrow was cellular, and the transplanted kidney showed no evidence of a rejection reaction.

Our surgical colleague, Dr. David Blumenstock, has performed orthotopic lung transplants in dogs receiving irradiation and marrow transplantation

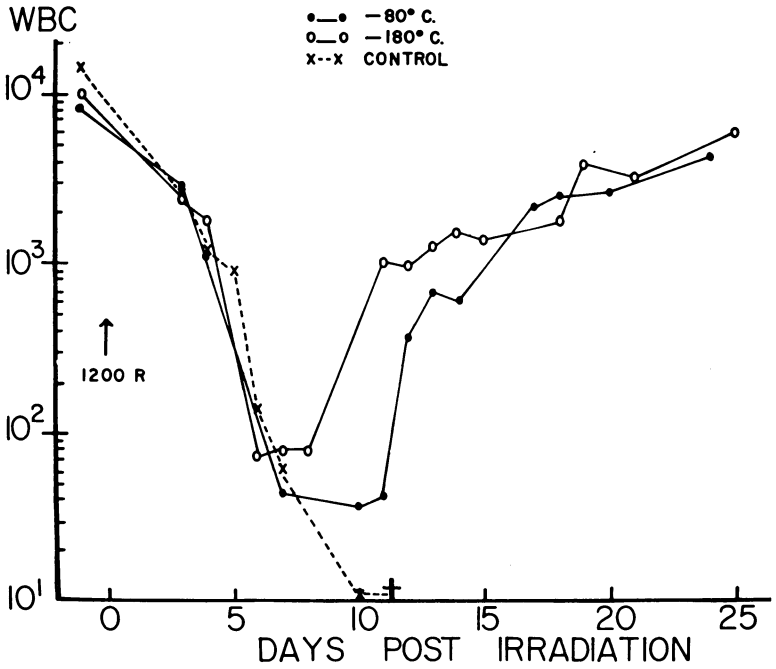

Fig. 15.—White blood cell counts in three dogs given 1200 r whole-body irradiation. Dog A823 received his own marrow stored for 14 months at —180° C. Dog A833 received his own marrow stored for 14 months at —80° C. The control dog received no marrow infusion. (*Transfusion*, in press.)

or methotrexate. Several of these dogs and their transplanted lungs have survived beyond 100 days.[30] Their difficulties, like those of Dr. Mannick's dogs, relate to the problem of restoring lymphocytic defences in an immunologically altered animal.

Radiation Protection

The LD_{50} dose of whole-body irradiation for man is estimated by many to be of the order of 400 r. The data presented here (Fig. 1 and Fig. 12) indicate that an infusion of isogeneic bone marrow can protect the irradiated individual against the effects of exposure three or four times this LD_{50} value. Since few individuals are fortunate enough to have identical twins, the usefulness of isogeneic bone marrow in radiation protection must refer to the individual's own bone marrow stored prior to radiation exposure. Satisfactory storage techniques are now available by freezing marrow in glycerol or dimethyl-sulphoxide. Fig. 15 presents the hematologic data in two dogs whose bone marrow was frozen in 15% glycerol 14 months prior to their radiation exposures.[31] One dog's marrow was preserved at –80° C., the other at –180° C. The dogs were exposed to 1200 r of whole-body irradiation. Note that both showed a rapid recovery in their white blood cell count. Both dogs are now clinically well three months after this lethal radiation exposure. A third dog that did not receive an infusion of bone marrow died on the 11th day. It appears feasible by present technique to carry out successful marrow storage in the case of individuals who are exposed to the risk of radiation accident. Obviously, a similar marrow storage can be carried out for patients who are about to receive a potentially lethal dose of irradiation in the course of treatment of malignancy.[32]

Chemotherapeutic Agents and Marrow Transplantation

Many of the chemical agents now in use for the treatment of cancer suffer from the limitation that they are toxic to the normal bone marrow. Protection against the effects of their marrow toxicities by post-treatment infusion of a stored sample of autologous bone marrow might be expected to extend the therapeutic usefulness of these agents. Studies of this variety have been made in man and in experimental animals.[33-36] The observations in man have been either difficult to interpret or, if interpretable, have shown no clearly beneficial effect of the infusion of marrow.[37] Studies in experimental animals are as yet rather incomplete. In our laboratory we have not been able to protect the mouse or the dog against a lethal dose of Thio-TEPA by subsequent infusion of isogeneic marrow. Apparently death in this instance is due primarily to toxic effects on organ systems other than the bone marrow. Further study is thus necessary before there can be a general clinical application of infusions of autologous marrow in cancer chemotherapy. Infusions of marrow will be of usefulness chiefly with treatment schedules and agents that place a primary burden on marrow function. Many agents cause damage to organs other than marrow, and these toxicities are not to be greatly remedied by implantation of marrow. In the course of this study it may be desirable to re-evaluate chemotherapeutic agents that have been rejected for clinical use because of a primary excessive toxicity to marrow.

SUMMARY

Efforts to explore in large animals, and to extend to man, clinical implications derived from a large body of radiation studies in mice have met with partial success. Marrow function that has been destroyed by radiation exposure can be restored easily by intravenous infusion of viable autologous (isogeneic) marrow cells. Cells for these infusions can be stored at low temperature for prolonged periods.

The transplantation of foreign (allogeneic) marrow is difficult and presupposes a careful destruction of the host's defence against foreign tissue. It requires also an adjustment of the successful graft's reaction against its defenceless recipient. Current investigations with chemicals that affect immune response offer encouragement to the hope that these problems of the transplantation of marrow and the somewhat similar

problems of the transplantation of whole organs may be managed eventually in a manner that is clinically acceptable.

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Clinical Evaluation of a Theophylline Solution (Elixophyllin) in Children with Bronchial Asthma

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THE clinical effectiveness of this water-alcohol solution of theophylline, Elixophyllin,* both in children and adults, has been reported earlier.[1-5] Blood levels of theophylline following therapeutic doses of this preparation were found to be higher than those obtained with other commonly used theophylline preparations.[6, 7] The preparation lends itself to very accurate dosage. Side effects and, in particular, gastric distress are reported to be infrequent.[8] For these reasons a clinical evaluation was undertaken.

MATERIALS AND METHODS

The drug contains 80 mg. theophylline and 3 ml. ethyl alcohol in each 15 ml. of the water-alcohol solution. All patients received 0.5 ml. per lb. body weight in each dose, which was given orally.

Clinical

House officers staffing the Emergency Ward of The Montreal Children's Hospital were asked to withhold adrenaline in cases of acute bronchial asthma and to treat the patients with the water-alcohol solution of theophylline. The clinical response was evaluated at 15 and at 30 minutes.

Respiratory Function Studies

The indirect maximum breathing capacity was measured in 10 patients in mild to moderate asthmatic attack and recorded in litres per minute. The maximum breathing capacity was calculated from the forced expiratory volume measured over the first 0.75 sec. after the start of a forced expiration, assuming a respiratory rate of 40 per minute. The maximum breathing capacity was measured before and again 30 to 45 min. after the administration of the theophylline preparation. After the second determination, the patients immediately inhaled a 1/200 adrenaline aerosol by mask for a maximum period of five minutes or until symptoms of sympathetic stimulation were noted. At this point, a final determination of the maximum breathing capacity was done. Three expirations in the standing position were measured for each determination. It should be noted that adrenaline aerosol is not administered therapeutically for this length of time in this clinic.

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