shortening, or safflower oil as the source of dietary fat.

Summary. Substitution of medium chain triglycerides (MCT) for coconut oil in a 15% fat diet fed to young chicks resulted in lower plasma and liver cholesterol levels, lower liver fat levels, and less body weight gain than were observed in chicks continued on the coconut oil diet. Plasma cholesterol was lower with corn oil than with MCT, but liver cholesterol was lower with MCT. Addition of cholestyramine to these diets reduced plasma and liver cholesterol levels with each of the dietary fats, but reduced liver fat only with the diet containing MCT. Cholestyramine did not significantly affect body weight gains.

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Patterns of Reconstitution of Neonatally Thymectomized Mice by Injections of Isolated Lymphopoietic and Hematopoietic Cells. (29762)

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Recent investigations have led to a better understanding of thymic function in neonatal mice. In these animals, the thymus is an active site of lymphopoiesis, and plays a critical role in establishing the integrity of the lymphoid system(1). Thymectomy in the newborn results in a striking decline in lymphocyte number in the peripheral blood, and in a marked atrophy of lymphoid tissues (2). As a consequence, a serious impairment of immunologic capacity develops, evidenced by a pronounced deficiency in the production of circulating antibodies following primary stimulation with several antigens, *e.g.*, sheep erythrocytes, Salmonella H antigen, killed influenza virus, and bovine albumin(2-4). In addition, neonatal thymectomy has been shown to be an effective means of protecting Swiss mice from the lethal effect of infection with lymphocytic choriomeningitis virus, by depressing normal hypersensitivity to this agent(5). The immunologic defect has moreover been demonstrated by using skin homografts and grafts of foreign cells, both normal and neoplastic(3,6-11). Neonatal thymectomy is also followed by a generalized wasting syndrome, characterized by progressive loss of weight, cachexia, lethargy, ruffled fur and diarrhoea, time of onset and extent of these symptoms and signs depending on the strain of mice(2,6,12).

Subcutaneous grafting of newborn or adult syngeneic or allogeneic thymus in neonatally thymectomized mice at 1 to 3 weeks of age reversed the changes in lymphopoietic tissues, abolished immunologic unresponsiveness, and prevented wasting disease(2,13). Thymic grafting as late as 3 to 4 weeks, but not at 6 to 7 weeks, has been found effective in preventing or reversing these changes(14).

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These results suggest that early in life the thymic graft contributes lymphocytes which are then seeded in the various lymphoid tissues. Nevertheless, it has been shown—at least in an allogeneic system—that the thymic graft is repopulated primarily by lymphatic cells of host origin(4,13). Furthermore, activity of the epithelial component of the thymus in lymphocyte production has been demonstrated in embryonic tissue(15,16), while evidence for the presence of a humoral factor in thymus inserted in diffusion envelopes(17,19) or chambers(12,18,20) which have been implanted in neonatally thymectomized animals has recently been reported. This would imply that lymphoid cells from post-natal donors which have already been under the maturing influence of the thymic humoral factor should also restore newborn thymectomized mice, whereas lymphoid cells from newborn donors should lack this ability. Indeed, it has been reported that syngeneic cells from thymus of 1-day-old donor mice, injected after neonatal thymectomy, did not prevent the pattern of wasting(8), whereas syngeneic lymphoid cells from 8-week-old mice, injected into thymectomized newborn, conferred immunity upon them, and prevented the stigmata of wasting(2,8,21).

The experiments reported here were consequently designed to ascertain to what extent newborn thymectomized animals were restored by injection of different lymphopoietic and hematopoietic syngeneic cells, and to follow the patterns of their restoration using several parameters.

Materials and methods. Mice of the highly inbred C3Hf/Lw strain were used. Whole litters, including both sexes, were thymectomized within 12 hours after birth. Thymectomized controls were kept without further treatment. Other thymectomized mice were injected intravenously one day later with one of the different cell suspensions, according to the following groups: cells from newborn thymus, adult thymus, lymph nodes, spleen and bone marrow. Syngeneic donors were used in all groups. Newborn thymic cells were obtained from mice less than 24 hours old. Donors of other types of cells were young adults of 4 to 6 weeks of age. Lymph node cells were taken from the peripheral (inguinal, axillary and cervical) lymph nodes. Bone marrow preparations were obtained by aspiration of the long bones (2 femurs and 2 tibiae from each animal) and suspended in medium No. 199. Lymph nodes, thymuses and spleens were removed aseptically, diced and gently pushed through a fine stainless steel screen (50 × 50 mesh). The cells thus obtained were also suspended in medium No. 199, and washed 3 times by low-speed centrifugation and successive removal of the supernatant. Finally, they were resuspended in the same medium, to achieve a concentration of 10×10^6 to 30×10^6 nucleated cells per 0.05 ml volume for injection. The injections were given intravenously 24 hours after thymectomy into the sigmoid portion of one of the transverse lateral sinuses of the brain.

Body weight was recorded at weekly intervals, with the exception of the animals receiving lymph node cells, this group having been injected at an earlier time in this series of experiments. Survival time was measured at 8 weeks of age, when the last of the thymectomized controls died. The survivors have been kept under observation up to the time of preparation of this manuscript. Total and differential peripheral white blood cell counts from tail blood were obtained at various intervals. Blood smears were stained with May-Grunwald-Giemsa. Antibody response was evaluated by titration of hemolysins and agglutinins at 7 and 14 days respectively after intraperitoneal injection of 0.1 ml of a 10 per cent suspension of washed, fresh sheep erythrocytes. Hemolysins were predominantly of high molecular weight (19 S), and agglutinins of low molecular weight (7 S) of antibody(22). A serious impairment of the capacity of neonatally thymectomized C3Hf/Lw mice to produce hemolysins to sheep erythrocytes has been noted (20). The graft-versus-host assay of Simonsen *et al*(23) was used for evaluation of immunological capacity of spleen cells of reconstituted mice from each group. This assay was performed as follows: Intraperitoneal injections of 20-30 × 10^6 dissociated spleen cells from intact or reconstituted C3H mice were made into all members of a litter of

(C57BL × C3H)F_1 hybrid mice, 8 days of age. There were at least 4 mice in each litter. Relative spleen weights (mg/10 g body weight) were obtained 8 days after cell injections when the F_1 mice were 16 days old. The spleen index was determined by dividing the mean spleen weights of F_1 mice receiving spleen cells from thymectomized but reconstituted C3H mice (parent) by the mean spleen weights of F_1 mice injected with spleen cells from (C57BL × C3H)F_1 hybrids (syngeneic) of similar age. The mice were autopsied when in poor condition or after death, and the absence of all mediastinal thymic tissue was ascertained by gross inspection, and microscopic sectioning where indicated. Any operated animal found to contain a thymic remnant was discarded from the experiment.

Results. The results of these experiments show that newborn thymectomized controls gained weight at a much slower rate than normal controls, and after the fifth week had developed all the signs of wasting disease. By the end of the eighth week there were no survivors in this group (Fig. 1 and Table I). The animals were depleted of leukocytes and the lymphocyte/granulocyte (L/G) ratio was reversed (Table II). Hemolysin response at 1 month was nil in the majority of the thymectomized animals (16 out of 25), or very low (9 out of 25) (Table III).

Mice injected with neonatal thymic cells exhibited a better pattern of growth than thymectomized controls. Yet at the end of the 8-week period their average weight was only 15 g (9 g lower than that of normal controls). Fifty-seven per cent of the animals survived for 8 weeks, while 5 out of 8 survivors died at a later date. Total and differential peripheral blood counts remained similar to those of thymectomized controls. Agglutinins to sheep erythrocytes were nil or extremely low in 5 out of 6 animals tested at 2½ months of age, but all the survivors in this group showed a normal titer when their

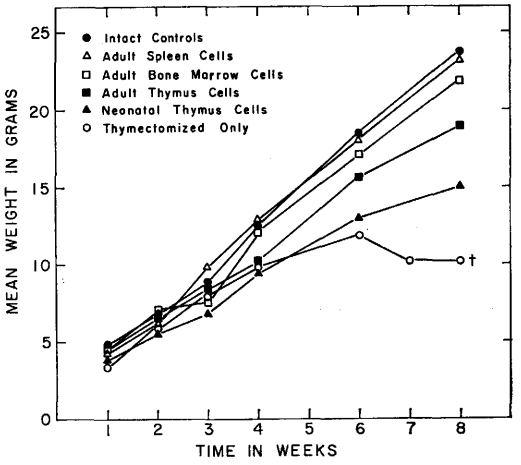

FIG. 1. Body-weight curves of experimental and control mice during first 8 weeks of life. (Animals injected with lymph node cells are not included.) Weights at from 8 weeks to 10 months showed the same trend.

TABLE I. Reconstitution of Neonatally Thymectomized Mice with Dissociated Lymphopoietic and Hematopoietic Cells.

Group	Strain	Treatment of recipients	No. & type of cells injected	No. & (%) survivors at 8 wk	Deaths of individual mice beyond 8 wk*
A	C3Hf/Lw	Neonatal thymectomy	None	0/35 (0)	—
B	"	*Idem*	18—20 × 10^6 adult lymph node cells	13/13 (100)	1 at 5½ mo
C	"	"	20—25 × 10^6 adult thymic cells	36/37 (97)	8 at 2½, 3½, 4, 5½, 6½, 6½, 7½, 7½ mo
D	"	"	10—30 × 10^6 adult bone marrow cells	18/22 (82)	3 at 3, 3½, 6 mo
E	"	"	10—25 × 10^6 adult spleen cells	35/35 (100)	7 at 3, 4, 4½, 5, 5½, 6, 6½ mo
F	"	"	15 × 10^6 neonatal thymic cells	8/14 (57)	5 at 3, 3, 3, 3½, 6 mo
G	"	None	None	43/43 (100)	1 at 7 mo

* Frequency of mortality in 8-10 mo period of observation ~ 30% among those reconstituted survivors not sacrificed for histologic study or for graft-*vs*-host assays.

agglutinins were tested at 4 months.

Neonatally thymectomized mice injected with adult thymocytes showed even a better evolution than those injected with thymocytes of the newborn. But they continued to grow at a slower rate than normal controls, having at the end of 8 weeks an average deficiency in body weight of 5 g compared with the latter. Thirty-six out of 37 survived this critical period, but 8 more died during the following 6-month period. Total blood count was in the normal range, but the L/G ratio remained reversed (28/72 at 6 weeks, and 42/58 at 9 weeks). Out of 7 animals tested at 5 months for hemolysins, 2 had very low titers and 5 were within the normal range.

Mice injected with adult cells from spleen, lymph node or bone marrow exhibited an ex-

TABLE II. Total Leukocytes and Lymphocyte: Granulocyte Ratios (L/G) in Reconstituted C3H Mice Thymectomized at Birth.

Group	No. of mice	Mean WBC & L/G ratios at: 4-5 wk	6-7 wk	9-10 wk	15 wk	21-24 wk
Neonatally thymectomized (no treatment)	35	5170 (26/74) (2000–10500)	—	—	—	—
Adult lymph node cells injected	14	6110 (38/62) (2950–11400)		5760 (29/71) (2400–10500)		10700 (30/70) (5900–14700)
Adult thymic cells injected	8	—	6880 (28/72) (4700–9500)	6800 (42/58) (3500–13000)	—	—
Adult bone marrow cells injected	5		—	7460 (44/56) (6300–12000)	—	
Adult spleen cells injected	8		—	—	8300 (47/53) (4000–12000)	10100 (30/70) (3700–18000)
Neonatal thymic cells injected	5		—	5520 (36/64) (3000–7200)	—	
Non-thymectomized controls	30	7320 (62/38) (4000–14600)	—	—	10200 (62/38) (7000–14400)	

TABLE III. Antibody Response to Sheep Erythrocytes in Reconstituted, Neonatally Thymectomized Mice.

Group	Treatment	0	1	2	3	4	5	6	7	8
				Hemolysins (19 S antibody) Response at 1 mo = ( ) and at 5 mo Reciprocals of log 2 dilutions						
Neonatally thymectomized	None	(16)	–	(1)	(7)	(1)	–	–		
"	Adult lymph node cells				(2)	2(3)	10(1)	(5)	1(2)	–
"	Adult thymic cells			1	1	–	3	2	–	
"	Adult spleen cells						1	1	1	2
Intact	None					1	2(3)	2(5)	1(7)	2(3)
				Agglutinins (7 S antibody) Response at 2½ mo; Response at 4 mo = ( ) Reciprocals of log 2 dilutions						
	Treatment	0	1	2	3	4	5	6	7	8
Neonatally thymectomized	Newborn thymic cells	1	1	3	–	–	(2)	1(1)	(1)	
"	Adult bone marrow cells			1(1)	–	3(2)	1(1)	3(1)	(1)	(1)
Intact	None						2(1)	7(4)	3	(2)

TABLE IV. Graft-Versus-Host Assay in (C57BL × C3H)F_1 Mice Using Spleen Cells from Thymectomized C3H Mice Reconstituted with Dissociated Cells from Various Sources.

Exptl group	Cells used for reconstitution	Age when spleen cells tested	Spleen indices	Mean index
Non-thymectomized C3H	None	5 mo	1.46, 1.46, 1.53 1.81, 2.14, 2.16	1.76
Neonatally thymectomized C3H*	"	5 wk	.95, .89, .73, .70	.82
Idem	17–25 × 10^6 Adult C3H spleen cells	5 mo and 8 mo	1.60, 1.97, 2.43, 2.63	2.05
"	10–25 × 10^6 Adult bone marrow cells	5 mo	1.16, 1.17, 2.05, 2.50	1.72
"	20–25 × 10^6 Adult thymic cells	5 mo and 8 mo	1.07, 1.15, 1.27, 1.67	1.29
"	11–15 × 10^6 Neonatal thymic cells	5 mo	1.26, 1.29, 1.65, 1.74	1.49

* Spleen cells tested at 5 weeks because of early death.

cellent trend of restoration as far as body weight curves are concerned. Percentage of survival at 8 weeks was high: 100% for animals injected with spleen or lymph node cells, and 82% for those injected with bone marrow cells. Nevertheless, a few animals in the various groups died at 3 to 6½ months following this period (1 out of 13 in the lymph node injected group, 3 out of 18 in the bone marrow group, and 7 out of 35 in the group injected with spleen cells). As in the previous groups, the cause of death was not apparent but in several of these mice a precipitous decline in body weight and peripheral blood lymphocytes was observed. These last 3 groups had normal total values of leukocytes in peripheral blood, though the L/G ratio always remained below normal (L/G ratio: 30/70 at 21-24 weeks in lymph node cell and spleen cell groups; 44/56 at 9-10 weeks in the bone marrow cell group). Hemolysin titers in the mice injected with lymph node cells were normal in all the animals tested at 1 month (13 animals), and at 5 months (13 animals), as compared with normal controls. The same could be reported on the 5 animals injected with spleen cells and tested at 5 months. Titers of agglutinin tested in animals injected with bone marrow cells at 2½ and 4 months (8 and 7 animals respectively) were fairly normal in most cases. The results of graft-versus-host reactivity of spleens from mice restored with adult and neonatal cells from the several sources are given in Table IV. It is clear that the reticular cells from these mice at the times they were tested have the capacity to provoke an immunologic reaction. Thymic cells appear less effective than adult spleen and bone marrow cells. It is clear also that restoration here was the result of colonization of the lymphoid tissues of the recipient thymectomized animal by the injected cells since a graft-versus-host reaction resulted.

Discussion. On the whole, these results show (1) that parameters such as body weight curves, survival rates, peripheral blood counts, and antibody response to various antigens, each considered separately, are not reliable enough to allow evaluation of the pattern of reconstitution of thymectomized animals injected with different cells. Consequently, all these criteria should be combined for a sound estimation of these results, and (2) that different lymphopoietic and hematopoietic cells have varied potentialities in restoring mice thymectomized at birth.

Though under the present experimental conditions thymocytes from newborn mice prolonged life in 57% of the mice beyond the 8-week period of survival of thymectomized animals, they failed in the majority of cases to prevent either subsequent death, or lymphatic depletion of blood and impaired agglutinin formation after sheep erythrocyte challenge. Total failure of thymocytes from the newborn to restore mice thymectomized at birth has been reported by Miller *et al*(4)

and Parrott and East(8). Yunis *et al,* by using a much higher number of newborn thymic cells introduced intraperitoneally reported immunological reconstitution by measuring graft-versus-host response(24). Confirmation is therefore necessary as to whether these apparently contradictory results depend on number of cells injected, strain differences, or other unknown factors.

The immunological competence of isolated thymocytes derived from adult mice was demonstrated by their ability to induce runt disease in newborn(25), and secondary disease in sublethally irradiated adult hybrid mice(26). In neonatally thymectomized mice, 10×10^6 adult thymic cells failed to restore homograft immunity(13). It has recently been reported that adult syngeneic or allogeneic thymocytes are able to reconstitute neonatally thymectomized mice in terms of graft-versus-host response(24), and capacity to respond to bovine serum albumin(27). The present work confirms this restoration ability in terms of survival rates at 8 weeks of age (97 per cent of the animals), in titers of antibody response to sheep erythrocytes, and in graft-versus-host reactivity. Nevertheless, it should be stressed that a moderate number of the animals (8 out of 36) died during a 7-month period of observation, and the L/G ratio remained reversed, as evidence of a relative lymphocytic depletion.

Lymph node or spleen cells from adult animals have been tested in neonatally thymectomized mice in relation to prevention of wasting and associated conditions. Injection of lymph node cells on the fifth day after neonatal thymectomy prevented wasting in 60% of C57BL mice(28). Administration of syngeneic spleen cells from adult donors provided restoration of homograft immunity and graft-versus-host reactivity(13). Wasting disease was prevented in C3H/Bi mice thymectomized at birth by injection of 4 to 5 million spleen cells intravenously(29). The results presented here are in agreement as far as body weight curves, antibody response and graft-versus-host reaction are concerned. Here, too, the reservation should be made that blood cell count of L/G ratios remained impaired, and several animals died in each of the 2 groups, in the absence of any obvious cause.

The results in the group treated with adult bone marrow cells deserve a special comment. These animals did not fall below any of the parameters considered in relation to the rates of restoration of those injected with lymph node or spleen cells. With the exception of a slightly impaired L/G ratio, and 2 out of 18 animals which died during the 6-month period of observation, they behaved normally in all respects.

Mouse bone marrow contains approximately 5% of cells which are morphologically identical to small and medium lymphocytes. In previous experiments, these cells have been shown to promote hematopoiesis and increase the population of erythrocytes(30).

By means of serial transplantation of bone marrow from mice exposed to X-irradiation, Cudkowicz *et al*(31) have shown that bone marrow lymphocytes are also able to stimulate hematopoiesis under given conditions. The present experiments on reconstitution with bone marrow cells, on the other hand, strongly suggest that this tissue contains cells with lymphopoietic capacity. In morphological terms, we can assume that cells of a lymphocytic structure in the marrow are those which initiated lymphopoiesis and restored the animals when injected into mice thymectomized at birth.

Whether the lymphoid cells in bone marrow which prevented lymphopoiesis and restored animals in this experiment are identical to the lymphoid cells which promoted hematopoiesis in the experiments of others referred to above, is still a matter of conjecture, and should be submitted to experimental proof.

Summary. The present results show that reconstitution of neonatally thymectomized C3H mice may be accomplished by colonization of the lymphoid tissues by injected reticular cells from several sites; these "stem" cells from adult and newborn donors have had the benefit of a thymic humoral factor. The low efficiency of newborn thymic cells may be the result of few "stem" cells as suggested by the results of Yunis *et al.* The considerable number of deaths of apparently reconstituted mice, nearly 30% in an 8-10

month observation period, suggest to us the likely possibility of depletion of "stem" cells in mice deprived of thymic tissue. The functional integrity of the thymus may indeed be necessary for permanent reconstitution.

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Growth and Cytopathic Effect of Rubella Virus in a Line of Green Monkey Kidney Cells.* (29763)

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Parkman, Buescher and Artenstein(1) and Weller and Neva(2) first described the isolation of rubella virus in cell culture systems. Cytopathic changes were, however, not observed in primary cultures of African green monkey kidney cells employed by the former who demonstrated multiplication of the agent by its capacity to interfere with ECHO 11 virus. Although Weller and Neva(2) showed that rubella virus is cytopathic for human amnion cells in primary cultures, the changes are slow to appear and only a few cells are visibly affected at a given time. With a line

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