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Prompt Need to Access the Maternal Effect(s) of COVID Vaccination on Her Young against Corresponding Strain

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1. Abstract

The major interest in materno-fetal relation is why fetus is not rejected by the mother, even in a different genetic background from the father. But in this article we have been investigating about the effect(s) of maternal antigenic stimulation or infection upon the active immune responses in her offspring. The results of various researchers have certainly pose significant problems as to the defense of infants against infectious agents, especially those introduced by their mothers. But we have already reported that maternal antigenic stimulation greatly suppresses the specific immune response of the offspring in a system of mouse vs heterologous erythrocytes and other T-dependent antigens. This suppression was antigen specific and effective on 1/6 life of rodents. The mechanisms that concerned in this suppression was not antigen administered nor antibody produced in the mother. The supporting evidence were that this suppression was MHC restricted and limited in during pregnancy between mother and her young. The system examined was separating genetic backgrounds that the haplotype was different in F2 family where half of the young were identical but not in remainder to the F1 mother mouse. Moreover, cytokine level in both mother and her young, IFN-γ levels was up-regulated in such a young whose mother was immunized with antigen. The significance of this phenomenon were accessed as biological and medical intervention e hypersensitivities, autoimmune syndrome for her young after birth. Especially for the mother and infant health care and prevention of Corona Virus pandemic.

2. Introduction

The currently held view of the immune system proposes generally acceptable description supported by evidence. There are two primary system, innate and adaptive. On the contrary to this defense system, the overwhelming problems of possessing this dual system, the innate and adoptive does not seem to guard or even prevent the development of one internal threat to survival, but direct to autoimmunity accumulate hypersensitivity.

Materno-fetal relations include various aspect of immunological affair connected to the development of immunological maturation to her young. The one of the major interests in materno-fetal relations is how the fetuses can be delivered in safe from the uterus in the immunologically risky environment. The other is what kind of effect of mother dealt with to her baby's immune capability after delivery.

The most important merit from mother were published by many researcher about the transferable immuno-globulins via uterus and/or her milk. These reported effects were revealed when an infectious immunity are necessary to the agents invaded to the baby.

This was the case in many species of mammals and at least half an year was effective to protect in human.

In the course of our line of studies, we confirm the new expansion of biological movement were the case between mother and her young with a neat mice system. The effect was limited period of pregnancy not by transferable mother antibody but more biologically significant system including immunological factors including immunoglobulins.

In this report, we prepared genetically confident mouse system and try to understand the significance as biological system in order to understand the fundamental effect of mother to her baby. During gestation, we try to access the immune capability of mother mice employing a identical system of MHC expression and try to establish a preventive combination of gamates for future succeed of the progeny [1]. In this review, we would like to introduce the materno-foetal relations employing simple genetical background of MHC complex, This standpoint of view promise to the safe delivery and safe growth of baby's life without autoimmunity and hypersensitivity. Moreover, this trial may pilot a safe combination of marriage to prevent so called morning sickness in pregnant mothers. In general, an aspect to the ontogeny of immune capability, the pregnant status is the critical time to start the ontogeny of the immune system under the genetically non-identical combination of her spouse, gene circumstance from mother and father. The introduction of new genes is important not only in the reproduction of the population but also in the limiting value of the litter size. Maintenance of mother is important in biological aspect essential for the future to develop fetuses in uterus who cannot develop without mother, large enough to rest her/his uterus. The size of the fetus became bigger in homologous relations than in heterologous ones [8-12]. In these situation, maternal cytotoxicity against to the fetus is induced only when genetic background as in MHC and minor HC is different. The development of immune system in young is attacked and modified under the influence of maternal immunological attack. In this article, we tried to know first when genetic background is identical in mother and her young, how is mother affect to the fetus [13-16]. The immunological intervention through the mother to the fetuses is a concern even in homologous as well as heterologous relations but the quality and the quantity may different [17-26]. Our interest is to focus on the acquired immunological effect of the mother to her young in an environment free from allogenic effects, in order to avoid transplantation immunity resulted in allogenic relations in mother and her young, syngeneic and specific-pathogen free animals were employed [13, 27, 28]. In our experimental system, maternal antibodies were transferred via the placenta and/or milk, suggesting that a mixed level of serum antibodies were in the peripheral serum [13]. In young mice, by using a conventional method to detect antibody levels, it is difficult to distinguish whether the origin of antibody molecules derived from the mother or her young [1, 13, 14]. Therefore, we employed a tentative method to detect active production of specific antibodies in the offspring using localized hemolysis in a gel assay originated and modified by Jerne [29, 30]. Using this method, sheep erythrocyte is famous for its antigenicity of T-dependent antigen and convenience for use in laboratory treatments. Ovalbumin was also employed as T-dependent antigen but soluble type of them that easy to introduce tolerance when it was used without adjuvant [28]. We also selected bacterial Lipopolysaccharide (LPS) and bacterial polymerized flagellin as T-independent antigen for this experimental system [31].

We have already reported that maternal antigenic stimulation greatly suppresses the specific immune response of the offspring in a system of mouse vs heterologous erythrocytes. But some reports showed that the immune responses in young were augmented as a results of maternal immunity [18, 19, 21]. As to a possible mechanism for inducing this suppression, it is generally suggested that antigen molecules or specific antibodies are transmitted from the mother to her offspring, and neonatal tolerance may be induced. In order to confirm this possibility, the soluble protein Antigen Ovalbumin (OVA), with or without adjuvant, was administered to pregnant mice [13, 27]. First, the immune responses of the groups of mother mice given OVA with or without adjuvant were identified, and then the immune responses of the two groups of the young were compared. Furthermore, the dosage effect of antigen or antisera given to pregnant mice was investigated with respect to the passive effect of immune response in their young. Based on the results thus obtained, a possible mechanism is discussed for the suppression of the immune response in the young, derived from mice stimulated with sheep erythrocytes (SRBC) and OVA with or without adjuvant [13, 27].

3. Experimental Model in T-Dependent Ag.

3.1. SRBC as Antigen and the Suppression in the Young

3.1.2. The immune status of mother mice and the effects on her young

Pregnant C57BL/6 mice were immunize with sheep red blood cells, ($2x10^8$/mouse) on day 10 of gestation. The mother mice induced maximum primary responses to SRBC at this amount of Ag, the offspring were then delivered and raised until they were young adults after which each group was immunized with an optimum amount of corresponding antigen. Even in such infant, 2-week-old mice, the response was good at about 80% in the maximum number of Plague-Forming Cells (PFC)/active antibody production in the normal control group [14]. However, in the experimental group whose mothers had been immunized with SRBC during pregnancy, these responses were completely suppressed, up to 20 weeks of age (1/6 of life span in rodent, Figure 1). The young possessed, however, a significant amount of serum antibodies to SRBC suggesting transfer from the mother [14]. To ascertain the effect of dosage on the relationship between the immune reactivity of mother mice and the specific immune suppression of their young, various amounts of erythrocytes were intraperitoneally injected into pregnant mice. When pregnant mice were stimulated with 10^8, 10^9 and 10^{10} SRBC, they produced a significant number of PFC by

themselves, but in such young, the active immune responses of their offspring were completely suppressed (Figure 1 & 2). When pregnant mice were stimulated with small amounts of SRBC (less than 10^7), they did not induce PFC, but the specific PFC development in the offspring from such mother mice was not completely suppressed.

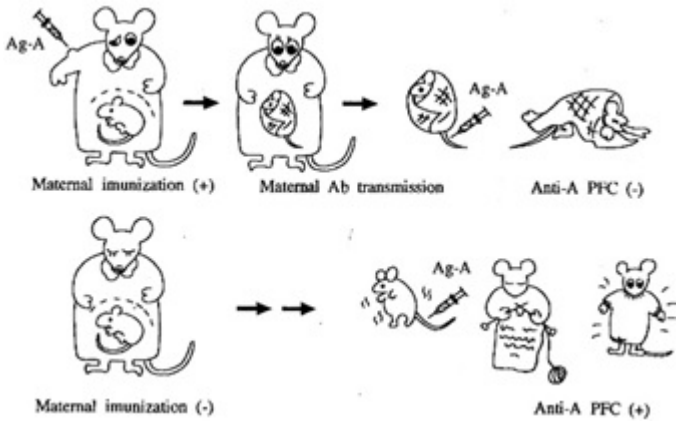

Figure 1: Effect of Maternal antigenic stimulation on the active immune responses in her young-diagram for experimental system
Pregnant mother mice were divided into two groups, the one was received antigenic stimulation (experimental group) and the other was not (control group). Both groups of the young mice were brought up to 6-8 weeks and then immunized with optimal amount of the corresponding antigens. The active antibody production was then detected by elegant but old-fashioned method so-called localized hemolysis in gel (or plaque forming cell ; PFC). After the antigenic stimulation, the experimental group did not respond to produce corresponding antibody, but the control group produce antibody forming cell that secret specific antibodies. This was the standard protocol of for accessing the maternal effect during pregnancy.

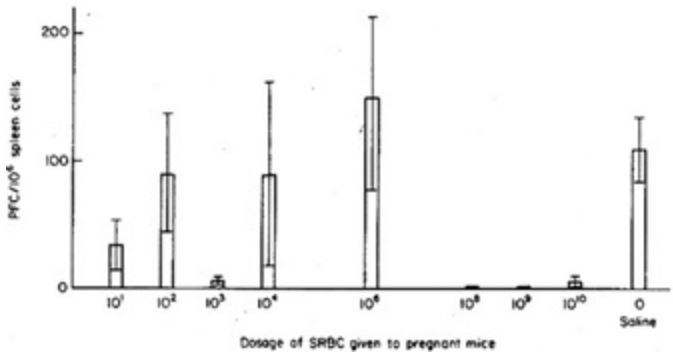

Figure 2: Effect of Maternal antigenic stimulation on the active immune responses in her young-Antigen amount for mother for induce the suppression.
After preparing the pregnant mice, various doses of antigen were administered via abdominal. 6-8 week later, their offspring were challenged to induce active immune response to heterologous RBC.

3.1.2. An effective time for the antigenic stimulation to the mother mice

In order to avoid the possibility of antigen transfer from mother to her embryo for this suppression, various stage of pregnant mouse were prepared and the active immune response was tested to the each offspring. The mother mice were line up from three day before fertilization to one day before delivery. In such mothers were administered optimal amount of antigen and all her young were immunized with corresponding antigen. As a result of this trial, both mother three days before fertilization and one day before delivery did not induce suppression in her young. These results indicated that antibody production process ant antigen itself were important to induce suppression in her young (Figure 3).

3.2 Ovalbumin as Antigen and the Effect of Adjuvant

It has been reported that a soluble protein antigen was a good inducer of suppressor cells especially when injected with high or low doses without adjuvant [13, 27, 32]. However in such antigen, it is possible to access the active antibody production by Plaque- Forming Cell (PFC) [33]. Under such a condition, there may be some factor in the suppressor cells that is transmitted from the mother mouse and establishes suppression in the young [34]. To test this possibility, pregnant mice were stimulated with large dosage/2 mg of soluble OVA without adjuvant in order to confirm the development of suppressive T cells in these mice [2, 3, 35]. Contrary to our expectations, the offspring responded normally after immunization with OVA 6-8 weeks after birth. However when pregnant mice were positively stimulated by OVA and the adjuvant $Al(OH)_3$, these offspring more effectively suppressed PFC development [27]. So it is concluded that this suppression simply affected maternal immune status. Rather, this suppression was well established when the mother mice was respond to antibody formation.

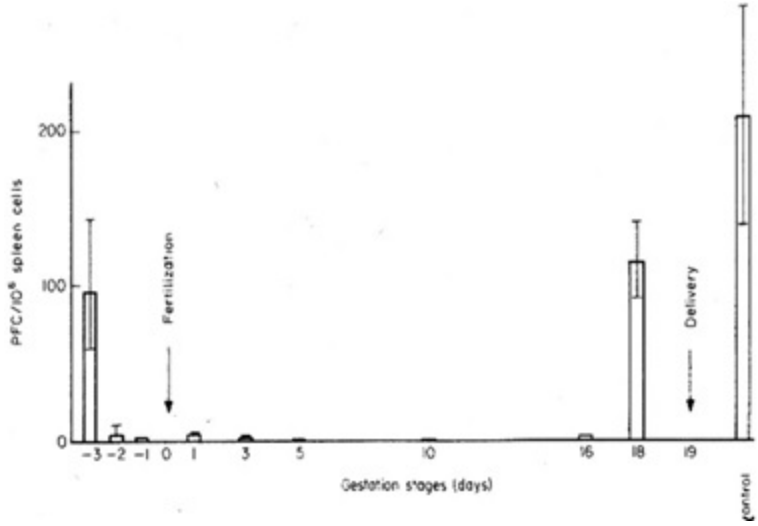

Figure 3: Effect of Maternal antigenic stimulation on the active immune responses in her young-the pregnant stage and the administration of antigen to the mother mice.

During the prepare for the pregnant mother, various stage of mother mice were administered antigen via abdominal. 6-8 week later, their offspring were challenged to induce active immune response to heterologous RBC.

3.3 Effect of Passively Transmitted Antiserum on the Pregnant Mice

The former experiment showed that only offspring from mothers stimulated with a large amount of SRBC were able to suppress the development of specific PFC. This data suggested that maternal transmitted antibodies to their young suppressed or discharged subsequent antigenic stimulation. To test this possibility, pregnant mice were injected with a specific antiserum via the tail vein once or several times during gestation. The antiserum was collected from the same strain of mice which was immunized with $1x10^8$ SRBC twice at an interval of 3 weeks. The titer of anti-SRBC level was as high as 1:1024. The control group was injected with a normal serum from the same strain of mice. The offspring were kept in an environment free from specific pathogens for 6 weeks after delivery. The offspring from mice injected with the antiserum during pregnancy showed only a slight suppression that was almost the same as that of the offspring from the control group [32, 33].

From our preliminary examination, anti-OVA PFC were only detected by injecting an antigen in the form of $Al(OH)_3$ gel twice at an interval of 2 weeks (the first with 200 μg and the second 20 μg). A single shot of OVA with adjuvant did not induce anti-OVA PFC. In order to test the effect of the different immune status of mother mice (especially PFC induction) on the induction of PFC suppression in their offspring, pregnant mice received primary stimulation from OVA with adjuvant, and were divided into two groups. One group received the booster and the other did not (the control group). The suppression of PFC development was not as strong in the offspring of mother mice who received a booster with the same antigen compared with that from the control group.

Together with the former data, these results suggest that some factors of the positive immune state of pregnant mice induced suppression of the immune response in their young.

4. Adoptive Transfer of Ab or Ag

The above result implied in part that transferred serum Ab suppressed the active response of the offspring [18, 19, 21, 34]. In order to test this effect of the passive transfer of antibodies, high titer of anti-SRBC, polyclonal antibodies or monoclonal IgG antibodies were injected via the tail vein of mice in their 10 day of pregnancy. The 6-week old offspring were then actively immunized with SRBC and developed PFC 5 days later. The experimental groups developed PFC at a slight lower rate (83%), but remained within the normal response range. The specific antibody transfer experiment showed a slight depression in the active PFC responses, but complete suppression of PFC response was not induced in the offspring whose mothers were passively injected neither polyclonal nor monoclonal specific Ab [35, 36].

We then tested the effect of antigen leakage from the mother to the fetus, in order to understand the induction of neonatal tolerance of the acquired immune response is the case or not in this system [32, 37]. Ovalbumin is a protein antigen that was tolelogenic itself, but became immunogenic when injected with the appropriate adjuvant. When BALB/C mice, which have a high responder to OVA were immunized with low to high doses of OVA without adjuvant, none of the mother mice responded to anti-OVA PFC even a after following an optimal OVA administration plus adjuvant. In the case of a high dose of OVA challenge without adjuvant to the mother mice, it is possible that an antigen molecule split off to the fetus and may have induced neonatal tolerance [37-39]. But in such a case, the offspring responded to anti-OVA PFC after delivery. On the other hand, when the mother mice were immunized with OVA antigen plus adjuvant, immunological memory was induced in the mother mice but the young did not respond following OVA antigen even if it included adjuvant. These results showed that an antigen fragment in the mother did not induce this suppression.

5. Foster Mother Experiment

Employing more natural system to test the transfer of antigen or antibody the foster mother experiments were designated. Pregnant mice were selected according to age and stage of pregnancy and divided into two groups. One group received antigenic stimulation and the other did not. On the day of birth, the young of both group were exchanged each other. Five weeks after delivery all the mice were antigenically stimulated by an optimal amount of SRBC. The results are as follows: the offspring nursed by the normal control mothers but delivered by the experimental mothers did not respond to further SRBC stimulation. On the other hand, the offspring nursed by the experimental mother but delivered by the normal mother responded well to further SRBC stimulation. Even when they possessed the passive transferred specific antibody, it did not affect this suppression [4] (Figure 4).

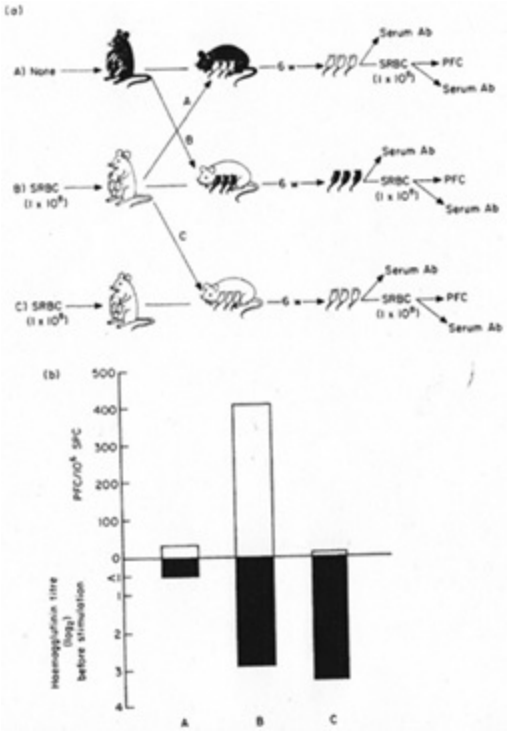

Figure 4: Effect of Maternal antigenic stimulation on the active immune responses in her young-the foster mother experiment between experimental and normal group.

During the prepare for the pregnant mother, almost same stage of pregnant mothers were divided in to two group. The one group was administered RBC (experimental group) and other was only physiological saline (control group). The two group of baby mice were mutually exchanged and brought up to 8 weeks. And then active antigen stimulation were carried out for each group of mice.

6. Adoptive Transfer of Effector Cells in this Suppression

Immune suppression is usually attributed to CD8 positive or so called suppressor cells [40-48]. In this suppression system, the effector cells were identified by the adoptive transfer system. This experiment was carried out in both the mother mouse and her offspring by preparing splenic nucleated cells separating into macrophages, T cells and B cells. The T cell population was further divided into CD4 and CD8 cells. Each cell suspension in offspring was adjusted from $1x10^3$ to $1x10^7$/0.2ml and adoptively transferred into the young normal mice via the tail vein.

The cell population analysis of her young showed that T cell populations were effector cells, but macrophage or B cells was not [43]. A further population analysis of the materno-foetal system demonstrated that CD4 but not CD8 cells were effector cells for this type of suppression [15, 49]. When young mice as a donors for the cell transfer, there were few reports of CD4 cells as effector cells for suppression [50-53]. The case for this suppression is that when we processed conventional cell analyses in SRBC-immunized mice that were the same age as the control young, the CD8 but not CD4 cells suppressed further antigenic stimulation in our laboratory as usually expected [45-48, 54, 55] (figure 5).

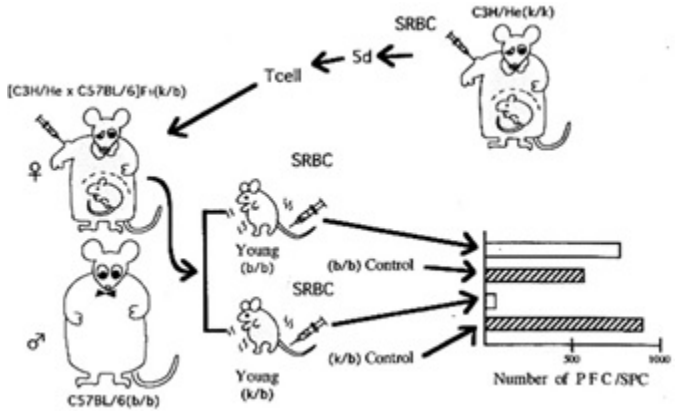

Figure 5: PFC and cytokine production in mother and her young in case of maternal immunization

To test the cytokine levels in both mother and her young, age-matched mother and age-matched young mice were immunized and then accessed the amount of IL-2, IL-4 and IFN-g. Among the cytokine tested in this experiment, IFN-g levels in the young whose mother was immunized with antigen. This results implied that the mechanism of the suppression in the young whose mother was immunized by antigen during pregnancy made functional bias to her young without simple affect by antigen or antibodies through her mother.

7. Maternal Immunization and Adoptive Transfer of Lymphoid Cells

7.1. Normal Pregnant Mice were Administered Cell Derived from the Immunized Pregnant Mice

The results show the basic schedules for maternal immunization of pregnant mice and PFC assay in the offspring. When the pregnant female mouse had been immunized intraperitoneally with $2x10^8$ SRBC, the production of anti-SRBC PFC in the offspring was completely suppressed. To determine which maternal lymphoid cells were responsible for this suppression of anti-SRBC PFC responses, adoptive transfer experiments were carried out also in mother. Pregnant female mice were injected intraperitoneally with $2x10^8$ SRBC on day 10 of gestation. Five or 6 days after the injection, the maternal peritoneal exhodate cell; PEC or SPC were transferred into other non- immunized pregnant mice on day 10-13 of gestation. The offspring of the recipient pregnant mice were raised for about 6 weeks and tested for their anti-SRBC PFC responses. Suppression was observed in the IgG PFC only when the recipient mice received 10^4 or more SPC from the immunized pregnant mice. A dose of 106 SPC yielded similar results in other experiments [one example is as follows: 1067±64 IgM PFC and 194±25 IgG-PFC/106 SPC in the offspring of the normal pregnant mouse(n=5), 1107±110 IgM PFC and 56±22 IgG-PFC/106 SPC in the offspring of the recipient mouse (n=7); $0.001<p<0.01$ in IgG PFC<. For the maternal PEC of the immunized pregnant mice, the same experiments were carried out and similar results were obtained. Furthermore, the maternal cells of the immunized pregnant mice were separated into T cells, B cells and macrophages, and transferred to other normal pregnant mice. Thus a pregnant female mouse was injected intra -peritoneally with $2x10^8$ SRBC on day 10 of gestation. Five or 6 days after injection, the maternal PEC or SPC was obtained from the pregnant mouse. The maternal SPC or PEC of immunized pregnant mice were separated into T cells, B cells and macrophages. Each type of maternal cell was transferred intravenously into other non-immunized pregnant females on days 10-13 of gestation. The offspring of the recipient pregnant mice were raised for about 6 weeks and tested for their anti-SRBC PFC production. The data shows the results in offspring of the pregnant mice that had received T cells, B cells and macrophages separated from the maternal PFC of the immunized pregnant mouse. The suppression of anti-SRBC PFC was observed only in the offspring of the recipient pregnant mice that had received T cells of the immunized pregnant mice by adoptive transfer. Such suppression was not observed in offspring from the recipient pregnant mice that had received other types of cells. Thus neither maternal B cells nor macrophages induced the suppression of PFC responses in the offspring of the recipients. With the dosage experiment, we tried to titrate the maternal T cells obtained from the SPC of the immunized mouse. Five 103 or more maternal T cells were required to obtain a suppressive effect on the PFC responses in the offspring, no such effect was observed with lower doses (15). In other experiments, maternal B cells were obtained from the SPC of the $2x10^8$ SRBC immunized pregnant mice and then transferred into the normal pregnant mice at the dose $2x10^4$ according to the same procedure. One example of the results is as follows: 521±71 IgM PFC and 190±60 IgG PFC, 174±29 IgG PFC (n=9) in offspring of the normal pregnant mouse. No suppression was observed in the experiments of B-cell transfer. These results showed that the maternal T cells of immunized pregnant mice are predominantly responsible for the suppression of PFC responses in offspring.

8. Maternal T-cell Subsets

We also investigated which subsets of the maternal T cells were responsible for the suppression of PFC production in offspring (91). The pregnant mouse was intraperitoneally immunized with the same dose of SRBC as above on day 10 of gestation. On the day 6 after immunization, nylon wool-purified T cells were obtained from the maternal spleen cells and separated into populations of maternal L3T4-depleted T cells, maternal Lyt-2-2-depleted T

cells and whole T cells. Each population of T cells was adoptively transferred into other normal pregnant mice in the same way. The production of anti-SRBC PFC was examined in offspring of the recipient pregnant mice in the same way as described above. No suppression of anti-SRBC PFC was observed in the offspring of the recipient pregnant mouse into which the L3T4-delpeted T cells had been transferred. On the other hand, suppression of PFC was observed in the offspring of the recipient pregnant mice into which the maternal Lyt-2-2- depleted T cells or population of whole maternal T cells had been transferred, suggesting that the maternal $L3T4^+$ T cells are responsible for the immune suppression induced by maternal immunization.

These effector population analysis in both mother and her young, showed that CD4 (Lyt2-2 depleted) cells were key cells for this suppression. But these cell populations itself did not suppressed anti-SRBC PFC when injected into the immunized individuals [15].

8.1 Maternal T cells induce suppression of PFC response in offspring in an MHC-restricted fashion

Above experiments implied the same subtype of T cells were effector cells in both mother and her young. Moreover maternal cell may difficult to cross the anatomical barrier between mothers to her young. Many reports concerned about immunological suppression, how the direct contact were important in the cellular cooperation [16, 61-73]. The mechanism of suppression still unclear so as to test the interaction of mother and her young, next we tried to test MHC-restriction is fact in this suppression or not [6, 31, 32, 33, 34, 35, 36, 37, 38, 39, 77, 79, 80, 81].

C57BL/6J (H-2b) pregnant mice were intraperitoneally injected with 2×10^8 SRBC/mouse on day 10-12 of gestation. Five days later, maternal T cells were obtained from the spleen of the immunized pregnant mouse and were adoptively transferred into the normal pregnant mice of $(C3H/HeJ \times C57BJ/6J)F_1$ on day 10-12 of gestation. The recipient mice had been back crossed with C3H/HeJ male mice. Accordingly, the H-2 haplotype expressed in the offspring was H-2 $^{b/b}$ and/or H-2 $^{b/k}$. they were raised for 6 weeks and then examined for the production of anti-SRBC PFC. Suppression of the anti-SRBC IgG-PFC responses was detected only in the offspring of H-2^{bxk} but not in H-2 ^{bxb}. In this experiment, the controls groups were the offspring of the F_1 pregnant mice that had been back-crossed with the C3H/HeJ male mice. The PFC responses were compared between the controls and the offspring of the recipient with the same haplotype. Reverse results were obtained in a reverse back-cross mating pattern [16]. Then C3H/HeJ pregnant mice were intraperitoneally injected with SRBC on days 10-12 of gestation. Five days later, the maternal T cells were obtained from the spleen of the immunized pregnant mouse and adoptively transferred into $(C3H/HeJ \times C57BL/6J)F_1$ pregnant mice that had been back-crossed with C57BL/6J male mice. The suppression of anti-SRBC PFC responses was found only in the H-2^{bxk} offspring among (C3H/HeJ ×C57BL/6J) F1×C57BL/6J from (C3H/HeJ×C57BL/6J) F1 recipients [16] (Table 1).

Table 1:

	G-type individual BYT		L-type individual STD	
	Before	**After**	**Before**	**After**
Total WBC (×103 µl)	6.85	5.78	3.83	5.03
Lymphocyte (%)	23.1	26.9	43.3	38.1
Granulocyte (%)	69.9	64.4	50.6	56.8
Neutrophil (%)	65.8	61.7	45.3	51.0
Eosinophil (%)	1.7	2.8	2.5	4.6
Basophil (%)	0.8	0.6	0.8	0.9

8.2 Maternal T cells generate a repertoire of suppressor T cells in the offspring

To test the above in vivo MHC-restriction between mother and her young in vitro, PFC development and blast genic responses [10-12] were induced in plastic dishes that were mixed with antigen presenting cells, T and B cell Combination with the cells from mother and her young.

A C3H/HeJ pregnant mouse was intraperitoneally injected with 2×10^8 of SRBC on day 12 of gestation. Maternal T cells were obtained from SPC of the immunized pregnant mouse 5 days after injection, and intravenously transferred at 2×10^4 cells/mouse into $(C3H/HeJ\ \ C57BL/6J)F_1$ offspring on day 10 of gestation. The offspring of these recipients were raised for more than 6 weeks. This maternal T-cell population had induced the suppression of anti-SRBC IgG-PFC in the offspring with MHC restriction [15]. The F1 offspring of the recipients were examined with respect to the MHC restriction of suppressor activity. T cells (T_{off}) of one $(C3H/HeJ \times C56BL/6J)F_1$ offspring from the recipient, Th of $(C3H/HeJ\times C56BL/6J)F_1$ and B plus accessory cells from C3H/HeJ and C57BL/6J were obtained. In this experimental scheme, T_{off} and Th were enriched with nylon wool column and purified by treatment with anti-Ia mAb and C`. T_{off} were cultured with 2×10^6 cells of Th, 5 × 106 SRBC-primed B plus accessory cells from C3H/HeJ or C57BL/6J mice and 108 SRBC. One example is shown as following, T_{off} suppressed the anti- SRBC PFC responses by the C3H/HeJ-derived B plus accessory cells but not C57BL/6J-derived ones. In order to confirm these results, a similar experiment was carried out in the reverse cross-mating pattern with adoptive

transfer [16]. In the reverse experiment, suppression was observed in the opposite direction. T_{off}, which were obtained from offspring of C57BL/6J recipients, suppressed the anti-SRBC PFC responses by the C57BL/6J -derived B plus accessory cells. These results suggest that the suppressor T cells among the T_{off} population were activated only when SRBC antigens were present and recognized in the context of the same MHC haplotype as the one utilized in the maternal T-cell responses of immunized pregnant mice.

Additionally, in the mating pattern, we examined whether the suppressive factor produced by T_{off} was restricted to MHC in the same fashion as described above. To test this idea, nylon wool-passed T_{off} and Th were purified by treatment with anti-µchain mAb and C`. Under this condition, Antigen-Presenting Cells (APC) and macrophages, of H-2bxk were present in the Toff and Th populations. Accordingly, T_{off} should have recognized SRBC antigens that were present in association with the k haplotype of MHC utilized by maternal T cells of immunized pregnant mice. T_{off} including H-2^{bxk} APC suppressed the anti-SRBC PFC production, particularly Ig-G-PFC, by both C57BL/6J -derived and C3H/HeJ -derived B plus accessory cells [17]. These observations show the suppressive factors produced by suppressor Toff function without MHC restriction.

8.3. Maternal Lymphocyte Trafficking

The Maternal immunization induced suppression of the active immune response in her young. The mechanisms which was involved in this suppression was not antigen employed or antibody produced in the mother stated above chapter, but CD4 positive cells in both mother and her young. Moreover, this suppression was the case in the relationship that was MHC-identical fashion between mother and her young. MHC restriction in cell to cell interaction is usually cognate interaction system [18-22]. In modern biological considerations, cellular size of materials is hard to across the placenta in normal condition. Adler reported that a mother cells could transfer to her fetus and also in the case between fetus to fetus transmission [23, 24]. Then we tried to test the cell transfer from mother to her young in our experimental system, the combination and MHC type and experimental design was shown in the Figure 6 & 7. We attempt to substantiate the presence of maternal cells in the foetal circulation through the use of molecular techniques. We found that highly polymorphic microsatellite sequence within the class II Eb gene of the H-2 complex is useful for the molecular detection of various H-2 allele. DNA polymorphic analysis was used for tracking maternal H-2 alleles in the spleen of baby mice. The main procedures involved polymerase chain reaction In amplification and restriction fragment length polymorphism analysis of the DNA sequence encompassing the H-2 specific microsatellite from genomic DNA of baby mice. The experimental results indicated that maternal T cell of immunized pregnant mice cross the placenta into the fetus, eventually inducing antigen specific immunological vias in her young mice [92, 93].

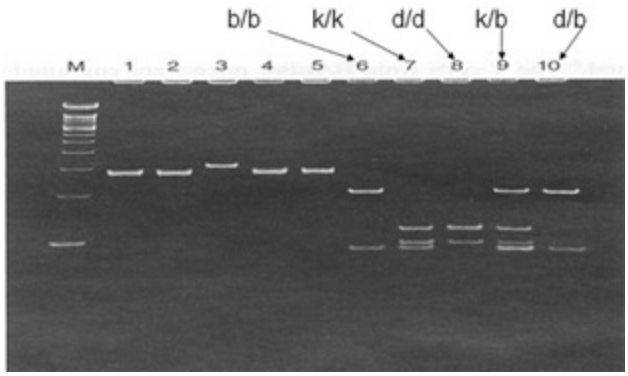

Figure 6: Polymerase chain reaction PCR) and Fnu4H I restriction pattern of three inbred and two hybrid F1) mice strain
Identification of H-2 haplotypes by PCR amplification and restriction fragment length polymorphism (RFLP) is shown in Fig 7. (8%PAGE). Lane 1-5 show the bands before treatment with Fnu4H Iand lane 6-10, the band after treatment with Fnu4H I. Lane 1and 6 showes the H-$2^{b/b}$ mouse, lane 2and 7 the H-$2^{k/k}$ mouse, lane 3and 8 the H-2d/d mouse,lane 4 and 9 the H-$2^{k/b}$ mouse and lane 5 and 10 the H-$2^{d/b}$ mouse. M,100-bp DNA ladder size marker (in bp): 2072,1500.700,500,400,300,200,100 from top to bottom, respectively.

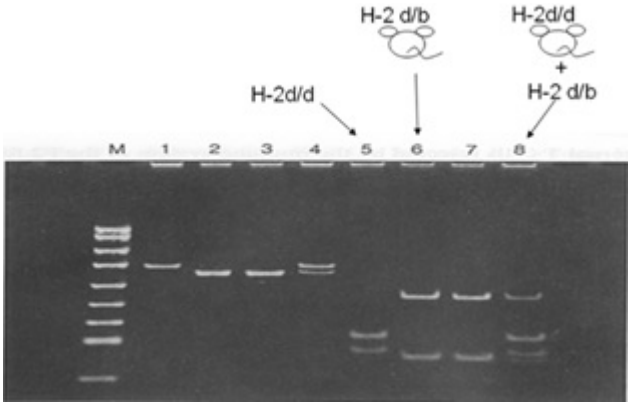

Figure 7: The H-2 $^{d/b}$ allele of the engrafted T cells can be found in the spleens of the F2 H-2$^{d/d}$ baby mouse.
Lanes 1-5 show the bands before treatment with Fnu4H I and lanes 6-10, the bands after treatment with Fnu4H I. Lanes 1 and 6 show the normal mouse (H-2^{d}, tail),lane 2 and 7 the normal mouse (H-2$^{d/b}$, tail). Lane 3 and 8 the T cell donor mouse (H-2 $^{d/b}$ tail),lane 4 and 9 the F1 normal mother mouse accepted immunized T cells (H-2$^{d/b}$, tail) and lane 5 and 10 the F2 baby mouse (H-2$^{d/d}$, spleen) alleles. M,puc19/MspI size marker. Note, in lane 5, the mother mouse's alleles(H-2 $^{d/b}$)can be resolved and lane 10,the H-2$^{d/b}$ restriction pattern (208-bp fragment and 85-bp fragment) also can be found.

9. Selection of Suitable TCM as Adjuvant for Virus Vaccine

So as to induce secretary IgA plus secretary piece in the local mucosal membrane, Suitable TCM is necessary to select as adjuvant for virus vaccine. As pointed out in the section, two major TCM [38, 39] are famous for increase and activate lymphoid cell, both granulocyte and lymphocyte. The prominent induction of viral vaccine composed with secretary IgA with secretary piece, it is necessary to preliminary confirmation is necessary employing at least by primate.

10. Immune Response is Associated with Diseases

10.1. Progress in Viral Infection

In the case of an acute viral infection in epidemics, the efficient virus-specific immune response is essential. A powerful reaction of helper T and cytotoxic T cells was generated to control and erase viral. viral-specific cytotoxic T cells show antiviral activity by producing IFN-γ and cytokine or directly killing the infected hepatocytes. B cells are co-stimulated by T cells and then produce antibodies against viral specific antigen. Virus infection refers to the extent and amount of antiviral immune response. Self-limited acute viral infection. CD16^{+} cells and CD16/56^{+} cells play an important role in the early control of the viral, and then a robust reaction of CD4^{+} T cells and CD8^{+} T cells is generated to control and eliminate viral. CD19^{+} cells, which are estimated by CD4^{+} T cells, produce anti-HBs, anti-HBe and anti-HBc. These protective antibodies remove viral antigens and viruses from the circulation and prevent or limit a viral infection. Chronic viral infection. Five stages are identified, including "immuno-tolerant" stage with high replication of viral DNA and low-inflammation, "immune-active" stage with viral-specific cytotoxic T-cell reaction and antibody production leading to chronic liver injury, inflammation and liver regeneration, "immune inactive" stage with low replication of viral and limited inflammation, "immune reactive" stage with chronic hepatitis, HCC. The late stage of "immune exhaustion". antigen (HBeAg) and viral nuclear antigen (HBcAg). These antibodies act to remove antigens and viruses from the circulation to prevent or limit virus reinfection. In addition, CD16+ cells and CD16/56+ cells efficiently control viral whose activities are achieved earlier than those of viral-specific T cells. In chronic viral infection, the early stage was described as "immune tolerant," with high replication of viral DNA and low inflammation in childhood. The progressive loss of immune tolerance leads to the "immune" stage with viral-specific effector T cell reactions during puberty, leading to chronic liver injury, inflammation and liver regeneration. Patients can then enter an "immune-inactive" stage with low viral replication and limited inflammation. A small part of patients in the inactive carrier stage are exposed to a viral relapse, which shows a replicative viral representation and thus enters the "immune reactive" stage with chronic hepatitis, which transitions to liver fibrosis, cirrhosis and HCC. In the late phase, a number of oncogenic signaling pathways activated by viral lead to immune flight and promotes the eventually developing HCC. More recently, studies have shown that viral-immune-tolerant patients develop HCC, while treated "immune-active" patients develop HCC at a lower rate. Together with more cumulative immune-mediated hepatocyte damage would be more susceptible to sensitive groups.

11. Pathology of Viral Disease

11.1. Immune Response Related to Disease Progression during Viral Infection

In the case of a self-limited acute viral infection, the efficient viral immune response is essential. A strong reaction of the helper T and effector T cells was created to control and delete viral effector T cells, showing an antiviral activity by producing IFN-γ and TNF-α or by directly killing the infected hepatocytes. B cells are co-stimulated by T cells and then produce antibodies against viral surface antigen/viral infections related to the size and amount of the antiviral immune response. Self-limited acute viral infection. CD16 cells and CD 16/56 cells play an important role in the early

control of the viral, and then a robust reaction of helper T cells and effector T cells is generated to control and eliminate viral. B cells, which are costed by T cells, produce anti-HBs, anti-HBe and anti-HBc. These protective antibodies remove viral antigens and viruses from the circulation and prevent or limit a viral infection. Chronic viral infection. Five stages are identified, including an "immuno-tolerant" stage with high replication of viral DNA and low inflammation, an "immune-specific" stage with viral-specific effector T cell response and antibody production leading to chronic liver injury, inflammation and liver regeneration, "immune inactive" stage with low replication of viral and limited inflammation, "immune reactive" stage with chronic hepatitis, passes over. Viral surface antigen and viral nuclear antigen. These antibodies act to remove antigens and viruses from the circulation, preventing or limiting virus reinfection. In addition, CD56 cells and CD16/56 cells efficiently go viral, whose activities are earlier than those of viral-specific T cells. In chronic viral infection, the early stage was described as "immune tolerant," with high replication of viral DNA and low inflammation in childhood. The progressive loss of immune tolerance leads to the "immune" stage with viral-specific effector T cell reactions during puberty, leading to chronic liver injury, inflammation and liver regeneration. Patients can then enter an "immune-inactive" stage with low viral replication and limited to inflammation. In particular, part of patients in the inactive carrier stage are exposed to a viral relapse, which shows a replicate viral representation and thus enters the "immune reactive" stage with chronic hepatitis, which transitions to liver fibrosis, cirrhosis and HCC. In the late stage, a number of oncogenic signaling pathways that are activated by viral signals develop, immuno-tolerant patients develop HCC, while treated "immune-active" patients develop HCC at a lower rate. In particular, patients with more cumulative immune-mediated hepatocyte damage would be more acceptable to the host cell.

12. Reviewed Sample for Virus Vaccine

While the intake of the HPV vaccine in the first few years after approval reflected and continues to increase the intake of other vaccines for adolescents, the rate of increase began to be delayed within three years of the introduction, which led to the countless controversies and concerns that have arisen during this time. In addition, there are still differences in coverage, with coverage between men being far regional and less coverage-wise. Nationwide, coverage for men and women ages 14 to 15 remains well target of 80% for healthy people, more than a decade. It is instructive to look at each of the factors that have put it on a trajectory, as opposed to that of the viral vaccine. Much of the logistical barrier to HPV vaccination could be overcome if a dose of the vaccine proves to be no worse than two. Currently, the combination of school entrance mandates and school-related vaccine administration programs would greatly facilitate access for adolescents in need of multiple doses, as would be the effect of the viral vaccine. Mandates also have economic benefits for individuals who could be expected to improve access in populations with the highest risk of HPV-associated cancers, as the vaccine entails high costs. Gender-neutral policies are called for to keep pace with rising absolute and relative rates of HPV-related cancers in men and would likely also encourage both women to normalize HPV vaccination by decoupling it from the culturally tense area of female sexuality in adolescents. The inclusion of men in government mandates can also help separate the vaccine from reports of autoimmune pathology and adverse effects on female fertility. Pharmaceutical companies and healthcare providers have the opportunity to convey a stronger gender-neutral message, and they are supported by research that identify the most successful means. While the global shortage of the HPV vaccine has recently led to calls to temporarily suspend gender-neutral vaccination efforts, alternative strategies for maintaining the supply of the vaccine, such as the suspension of vaccine Marketing to older cohorts, mitigating efforts to vaccinate men in the face of low national intake rates and the changing epidemiology of HPV-associated cancers. Finally, the younger age of vaccine administration, if approved, can also help to allay concerns about safety and news regarding adolescent sexual behavior. While gender-neutral mandates for mandatory HPV vaccination, coupled with improved access, would mitigate many of the factors that have limited intake, the same factors have led to any push by state legislators for the School entry almost eliminated. Vaccination requirements. Most public health boards have mechanisms in place to issue mandates, as has happened, and this could be a more durable way for this vaccine. Nevertheless, efforts to push for mandates for the HPV vaccine and future vaccines currently under development are likely to be increasingly supported by the perception of a landscape-saturated public health landscape with prescribed vaccines which is an ever-increasing burden on parents, children, children, and school administrators. The artificial vaccine came onto the market in a much different climate than the viral vaccine two decades earlier. The number of recommended vaccines had roughly doubled in the meantime. At the same time, the spread of vaccine protection advocates via the Internet and social media platforms around the world has contributed to the rise in vaccination hesitation. Vaccines that will be approved in the coming years will face similar struggles for support, given common characteristics of viral and viral vaccines in terms of transmission. Pharmaceutical companies and proponents of these vaccines must be careful to ensure that the intervals between, recommendation and mandate proposals are used effectively to educate the public and healthcare providers, address access issues, and create more complete safety profiles after the mass implementation of vaccine programs. Explanation of the author's publication All authors certify that they meet the public criteria for authorship. At the same time, there is a reason for parents' rejection of the vaccine, which is "not necessary" for their child, and the reluctance of many prompt care providers to

express their concern with parents, reflects the unease about the sexually transmitted nature of HPV infection. Almost immediately after the vaccine was approved, a moral dimension was prominent in the debates about its merits and the policies associated with it. Remarkably, anti-vaccination activists have prevailed in the past, both among politically liberal groups that focus on natural approaches to maintaining health, and among conservative groups that focus more on individual autonomy, but policy arrangements have been more drawn to the HPV vaccine and mandate proposals, with more conservative commentators rejecting mandates, often by focusing on parental autonomy on sexual health and education issues. Belonging to religious groups and more frequent worship visits have also been associated with the rejection of the HPV vaccine or the preference of the older age in vaccination. These political and religious associations can be seen as a reflection of perceived irreconcilability between HPV vaccination and messaging around abstinence and sexual permeability. The effects of these reservations, in turn, are amplified by the perception of suppliers of them, which, as there are, leads them to anticipate resistance and to recommend the vaccine less strongly than other vaccines.

13. Discussion

There were many reports and consideration based on the experimental and bed-side implication that the effects were many on her baby. The effect resulted in the allogenic relation was to consider to be serious to keep infant safe in the uterus. But in this article, even in a relation syngeneic, there was significant effect for her baby to suppress active immune responsiveness after delivery. This suppression was the case in rodents, mouse, rat and guinea pig in 1/6 of life-span. If it may possible to expand mouse systems into humans, the suppression is affect about until 13 years-old, even transferable maternal Ab is effective for baby a year, after birth. Including above implications, this phenomenon is serious and worthy of future investigation, when suitable test scheme is available in human. It is tempting to assume that two major possibilities may be involved in this suppression. First, either the SRBC or their stroma may be transferred to the foetus nor newborn. Secondly, maternal antibodies may also be related to this suppression, because the inhibitory effect on the PFC development was reciprocally related to the specific antibody levels before antigen stimulation in newborn mice. The transmission of maternal antibodies may account for the inhibition of antibody formation, as a result of discharging or masking the antigenic determinants [25]. In another system, the allogeneic new system, the maternal antibodies suppressed the infant immune responsiveness [26, 27, 28]. However, in our syngeneic system, the effect of allogeneic antibodies was avoided in this suppression. According to the results obtained the maternal antibody seems to affect the offspring. However, the possibility may be less likely in the light of the following observation. The offspring of the experimental group fostered by normal mother did not respond with following antigenic stimulation and no specific antibody was detected. Only from this result, there still remains a possibility that there were sufficient antibodies transferred which were not detectable by haemagglutination or hemolysin methods. They could opsonize and facilitate removal of SRBC before induction of T and B lymphocytes could occur. However, the normal offspring fostered by the stimulated mother responded well, even though the specific antibodies were detected in significant levels. The experimental offspring stimulated through a pregnant mother were inhibited without any effect of postnatal serum antibodies. Moreover, from the effective timing experiment concerning gestation period and antigenic stimulation, the group of young whose mother was stimulated 3 days before fertilization were not suppressed. In this group fetuses developed in an environment filled with specific maternal transferrable antibody. However, from a dosage experiment of mother mice, the anti-SRBC PFC were induced by the stimulation with 10^8-10^{10} SRBC. The offspring whose mothers were stimulated with such a high dose of antigen were suppressed completely. From these results, it is reasonable to conclude that factors which were induced during antibody formation were concerned with this suppression, including specific antibody. This suppression in the young continued for at least 15 weeks after birth, indicating that the mice were suppressed for about the first one-sixth of their lives. Functional subsets of the T helper cells, Th1 and Th2, are able to be identified by the types of cytokines they produce [2, 29-32]. The Th1 cells preferentially secrete IL-2 and IFN-γ, while the Th2 cells make IL-4 and IL-5. The proportion of Th1 and Th2 T cells in the lymphoid organs determines the type of immune response in an individual [33, 34]. While Th1 cells participate in cell mediated immune reactions the Th2 cells mediate humoral immunity and both types participate in cross regulation [35-39]. During pregnancy it has been reported that the overall direction of cytokine profiles is biased toward a type 2 response [2]. The significance of this change would be to interfere with the maternal rejection through the cell mediated immune system of histo-compatible fetuses [2, 3] by influencing the direction of maternal central lymphopoiesis as well as peripheral immune responses [2, 4, 5]. It is well known that multiparous mothers can develop high titers of cytotoxic antibody against paternally derived antigens, but this antibody does not destroy the fetus.

All creatures in the world, including humans, pose a risk of immunodeficiency in daily life. The factors that influence acquired immune activity are systemic metabolic disorders such as diabetes, malnutrition, extreme stress, senile and side effect due to cellular activity in cancer cells. So we have to choose a suitable menu every day to regulate immune function by leukocyte storage. The menu was summarized and listed as CAM: complementary and alternative medicine. One of the most important menu is TCM [33-37] in the Western medicine world, some trying to integrate Western Medicine and Eastern Medicine. We have tried to regulate the

immune response by much ripe for fragile daily state of stress and so on. The main menu was acupuncture, hot water hydrotherapy, light exercise, etc. In this article, we want to highlight the regulatory mechanism of hot source hydrotherapy. The circumstance of balneotherapy with the effectiveness of hot spring hydrotherapy, with the exception of cases of contraindication, has been medically beneficial approved to be effective in many stress-related disorders and improving the dysfunction of biological rhythm disorder as well as chronic diseases. The mechanism of effects has been reported in many studies, but many things are still unclear. Repeated stimulation can cause fatigue or regulation of the nervous system. Fatigue refers to the decrement of the reaction with repeated stimulation. The reports showed that the cutaneous mechanoreceptors in excitability as a result of repeated mechanical stimuli by sensitization refers to the reaction increments from novel, moderate heat stimulation, and it is the main phenomenon in the hypothalamus system. According to HSH [13-29] research, some of the volunteers reported to places on the body that were controlled by hearing, and they felt strong heat or heat during HSH, which spread around the stimulating location. Since the occurrence of this thermal sensitization reaction is often associated with obviously better therapeutic effects, HSH has often been used to treat various types of symptoms. Although the thermal sensitization reaction depends mainly on the selection of the sensitive for association with pathological condition, can also be a beneficial way to promote the effectiveness of hot source hydrotherapy.

14. Conclusion

This report suggested that the establish a better virus vaccine innovates from classic vaccine preparation

1) Antibodies against the virus limited to prevent syndrome.

2) It depend on the immunoglobulin (Ig) class.

3) Repeated antigen stimulation induce secondary response that mounted by IgG antibodies.

4) Hemopoietic herbal decoction may play an adjuvant for induce viral vaccine.

5) Serum IgG attacks virus together with host cell that share the room in the host.

6) The immunoglobulin class A, IgA, with secretory piece, is the most important for the development of the newly developing viral vaccine.

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