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**THE RELATION OF INFLUENZA IN PREGNANCY  
TO CONGENITAL DEFECTS**

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## INTRODUCTION

It is the purpose of this paper to give a comprehensive review of the literature concerning influenza in pregnancy as a cause of congenital defects. Included will be historical background, epidemiological and statistical studies, animal experiments, pertinent virological aspects and a critical analysis of information obtained.

## HISTORY OF INFLUENZA AND ITS RELATION TO PREGNANCY

The historical background of influenza dates back to 412 B.C. Hippocrates and Levy, at that time, elude to a flu-like illness in their writings. References to influenza are again found in the 15th and 16th century literature, but extensive interest in this disease did not occur until the end of the 19th century.<sup>4</sup>

Early theories as to etiology and treatment were varied and interesting in light of our present day knowledge. Benjamin Lee mentioned a few theories in 1891. He said that some authors thought that influenza lowered the vitality of tissues so that they were not able to resist onslaughts of the microbes of various diseases, and that any that happened to present found an entrance and developed their peculiar affection. Others thought that atmospheric conditions affected membranes of air passages and made it easy for germs to find entrance into the blood. A theory held by Lee and shared by a few others was that, "morbific influence whether germ, microbe, or occult meteorological departures from normal conditions, spends itself directly on the nervous system, and more particularly on the vegetative portion of that system or to particularize further, upon the pneumogastric nerve with partial implication of the spinal cord." This is why, he says, "the nervous prostration is out of proportion to the catarrhal disturbance."

Dr. Tezzier of France claimed that influenza was caused by a microbe called streptobacillus, whose habitat was putrid mud.

Some examples of treatment at the time are: strychnine, caffeine, alcohol, ammonia, quinine, salicylate of sodium and phenacetin.<sup>22, 23</sup>

Influenza was thought to be caused by a bacterial organism from about 1892 until 1918. Ball, in 1918, raised the question whether bacillus abortus of Bang was identical with influenza. However, in the same year there was some scepticism about influenza being caused by bacterial organisms in the German literature and the influenza virus was isolated in England.

The course of influenza in pregnant women is referred to in 15th century writings and after the flu epidemics from 1889-1891. The great epidemic of 1918 brought a flurry of articles in the literature with several studies of its influence in pregnancy. John W. Harris and P. Brooke Bland conducted extensive statistical research.

John W. Harris made a study of 1350 cases of influenza in pregnant women. His results revealed that, of the 1350 cases, the pregnancy was interrupted in 460 instances, 302 of these had been complicated by pneumonia. He made no mention of abnormalities in the children who were born of these mothers.

Bland stated in his article that pregnant women with influenza were more likely to abort or miscarry. Of the 2000 cases of influenza in pregnant women, that he reported, 31% died. He emphasized the importance of pregnant women being confined. As in Harris' report, nothing is mentioned in Bland's article about the condition of fetuses that were aborted or abnormalities in the infants who were subsequently

born to the mothers who survived the epidemic.

Interest in viruses as a possible cause of congenital anomalies was sparked by an Australian ophthalmologist, Gregg, in 1941. He pointed out the high association of congenital anomalies with rubella in the first trimester of pregnancy. His figures were too high compared to later studies but he laid the ground work for further research. It was only a matter of time until people became interested in other viruses as possible causes of congenital defects.

#### STUDIES PERTAINING TO RELATION OF INFLUENZA AND CONGENITAL ABNORMALITIES

Dogramaci and Green in 1947 published a study on the etiology of congenital heart anomalies. Some of their data was obtained from records of all patients with congenital heart disease seen in infants and Childrens Hospitals in Boston from 1936-1945. Of the 434 patients studied, 9 of their mothers had a clinical history of a virus infection in the first trimester. One of these 9, had a history of "virus-grippe" in the first trimester. This child had an atrial septal defect and tracheo-esophageal fistula.

McDonald carried out an investigation in Watford from 1952-55 and in St. Albans for 6 months in 1954-55. 3,295 women were interviewed at the hospital and prenatal clinics by a doctor and two public health nurses for a description of the first trimester of pregnancy. Illnesses were divided into several categories. One of the categories was acute febrile illness, defined as febrile if the woman was known

to have a temperature or complained of sweating. 86% of the acute febrile illnesses were respiratory. They further broke down their categories into acute specific fevers in which was included mumps, rubella and jaundice. Influenza was not listed. Of all the women, interviewed, there was an incidence of 31.8% congenital anomalies at birth.

The first definitive publication as to the effects of influenza on the fetus was by Campbell and Belf in 1953. Their study was in regard to the epidemic of A-prime influenza in Northern Ireland in December and January 1950-51. All the mothers attended antenatal clinics of the Belfast City Hospital, the Royal Maternity Hospital, Belfast, and Maternity and Child Welfare service of Belfast corporation. Their last menstrual periods were between September 1, 1950, and January 31, 1951. Each mother was questioned whether she had had influenza. At birth, classifications were made: 1. Normal still birth, 2. Deformed still birth, 3. Normal Live birth and, 4. Deformed live birth. There was a total 989 births, 164 of these were from mothers who said they had had influenza. Campbell and Belf concluded that there was no increase in abnormalities.

Pleydell made an epidemiological study of gathering materials from hospital birth registers, domiciliary birth registers, infant mortality registers, midwife and health visitor records, obstetricians, pediatricians and records of handicapped pupils from the school health department. The records were obtained in Northamptonshire from 1944-1957. 43 cases with history of influenza were found and



12 of these were in the first trimester. Of the infants born to these mothers, one had hydrocephaly, one aborted at 4 months and one aborted at six months.

The great world wide epidemic of Asian influenza in 1957 furnished abundant material for studies in pregnant women. Articles were published all over the world but the main research was done in American and the British Isles.

The most extensive studies in the British Isles were done by two groups. One group consisted of Doll, Hill, and Sakula. The other group consisted of Coffee and Jessop. The epidemic in Great Britain occurred between mid-September and late October.

Doll, Hill, and Sakula collected data from patients who attended the antenatal clinic at Central Middlesex Hospital between November 29, 1957, and March 7, 1958. Each woman was asked: 1. whether she had the flu, 2. whether she had stayed in bed and, 3. whether she had consulted a doctor during the illness. As a result of the screening, 128 were accepted as having had influenza. Of the 128, the diagnosis had been confirmed by a doctor in 49 cases. 47 were not accepted as having had influenza. The findings in the children born to these mothers were as follows:

- A. Diagnosis Confirmed by a doctor--49 cases and 50 infants.
  - 1. One with harelip and extensive nevus of the face (the mother had influenza 2 months before her pregnancy)
  - 2. One with an extra digit (mother had influenza 2 months to 3 weeks before pregnancy)

- B. Women with influenza not confirmed by a doctor
  - 1. 41 had influenza during first trimester
  - 2. a. one still born
    - b. one with hypospadias
    - c. one with congenital heart defect and cerebral hemorrhage
- C. Women not accepted as having influenza--48 children
  - 1. One stillborn infant

Coffee and Jessop's study was divided into two parts. Part I of their prospective study was published in 1959, and part II or their follow-up study was published in April, 1963. Their subjects were obtained at the antenatal clinics in three Dublin Hospitals between October 1, 1957, and October 1, 1958. These women were asked if they had had influenza. Women at the same stage of pregnancy who attended clinic the same day were used as controls. Every effort was made to match the controls as to age, parity, ABO and Rh groups. The condition of the baby was reported at birth of both the influenza and control groups. There was a total of 671 influenza infants and 672 control babies. In the total group of mothers with a history of influenza, there were 2 miscarriages and in the control group there were 3 miscarriages. In the influenza group, there were 24 or 3.6% malformed children and in the control group there were 10 or 1.5% malformed children. There were 18 stillborn children in the influenza group, 6 of which were malformed and 19 stillborns in the control

group, 3 of which were malformed. A history of influenza was recorded in the first trimester in 99 of the 671 influenza babies. Of these 99, 8 were malformed or 7.4%.

In Coffee and Jessop's follow-up study three years later, they were unable to locate 143 in the influenza group and 127 in the control group. 34 in the influenza group had died after birth and 22 in the control group had died. There was still a greater number of defects in the influenza group but the margin had narrowed. Of the total number traced, there were 15.2% abnormal children in the influenza group versus 10.2% in the control group.

Of those who were ill in the first trimester they found 7.2% abnormal children in 1957-58 and 33.3% abnormal children in 1961-62.

They found a preponderance of central nervous system defects in the influenza group. See the table below:

	<u>Influenza Group</u>	<u>Control Group</u>
Anencephaly	10	3
Spina Bifida	4	1
Meningomyelocoele	3	2
Hydrocephaly	2	2
Mongolism	6	1
Mental Deficiency	$\frac{1}{26}$ (8 in the first trimester)	$\frac{0}{9}$

The Asian influenza epidemic reached America, also in 1957. As in the British Isles, several doctors took advantage of the opportunity

to investigate the relationship between influenza and congenital defects.

Walker and McKee published a study done at the University Hospital, at the State University of Iowa in 1957. Their subjects were 439 patients who delivered at the University Hospital from February to May 1958. The subjects were divided into three groups: 1. patients who reported a febrile illness which might have been flu, 2. patients who had children with fetal anomalies but no history of an influenza-like illness and, 3. 101 consecutive patients with no particular history of a febrile illness. A 10cc blood specimen was drawn from each patient for hemagglutination-inhibition antibodies and neutralization antibodies as detected by mice against Asian influenza. Walker and McKee's reason for drawing only one blood specimen was based on Mulder and Masurel's opinion that at the time of the epidemic in June, 1957, the disease was new to everyone except older people. Therefore, they felt there should be no immunity and no specific antibodies present in their group studied.

The modified Salk test<sup>27</sup> was used for the hemagglutination-inhibition test and the Reed and Muench's method was used for detecting neutralizing antibodies. Eleven strains of Asian influenza were isolated from cases in Iowa City in 4-6 egg passages. One of the eleven strains was adapted to mice by intranasal passage and used to detect neutralizing antibodies against one of the eleven strains of virus.

In the hemagglutination-inhibition test, if the result was

positive, the titer was recorded. If the result was negative, the serum was tested against a second strain until a positive titer was obtained or the serum had tested against all eleven strains. Only 23 sera were selected to check for neutralizing antibodies. There was a general correlation between hemagglutination-inhibiting antibodies and neutralization antibodies i.e. when the hemagglutination-inhibition titer was high so was the neutralizations titer.

Results of their study revealed:

- A. 297 mothers
  - a. 53.2% gave positive history for influenza
  - b. 97.4% had positive serum reactions
- B. 31 patients who had children with fetal anomalies or part of a spot check. No history of influenza
  - a. 30 had antibody titers against influenza
- C. 101 consecutive patients
  - a. 100% positive reactors to hemagglutination test with several strains
- D. Congenital anomalies in 398 patients
  - a. 33 per 1000 live births
  - b. Only one of the above 33 reported having influenza in the first trimester

In the same year, Wilson, Heins, Imagawa and Adams in Los Angeles published a study of Asian influenzas effect on infants born approximately 9 months after the epidemic there. They also attempted to correlate hemagglutination-inhibition titers (determined by Salk's

procedure), influenza-like symptoms and congenital defects.

The blood specimens were drawn in the second trimester. The hemagglutination antigen used was pooled allantoic fluid with influenza A/Asian/Japan.

Their study showed that the history of illness showed only a chance relationship to titer, and physician-diagnosed influenza, as well, was not significantly related. Their results are tabulated Tables I and II.

TABLE I

Association of HI Titers with History of "Flu-like" Illness in 126 Pregnant Women

Symptoms	Neg.	1:5	1:15	1:20	1:30	1:40	1:60	1:80	Total
Influenza	18	2	2	7	5	5	0	1	40
Family contact with flu and cold	1	0	0	0	1	0	0	0	2
Family contact with flu but no symptoms	2	1	0	0	0	0	0	0	3
Flu vaccine given no illness	0	0	0	1	0	0	1	0	2
Few colds	9	4	4	10	2	3	0	1	33
Frequent colds	5	0	0	2	0	0	0	0	7
Fever or myalgia	2	2	0	0	0	1	0	0	5
Diarrhea	2	0	0	0	1	0	0	0	3
No symptoms	12	2	2	4	5	3	1	1	30
Unknown	0	0	0	1	0	0	0	0	1
<b>Total</b>	<b>51</b>	<b>11</b>	<b>8</b>	<b>25</b>	<b>14</b>	<b>12</b>	<b>2</b>	<b>3</b>	<b>126</b>

TABLE II

Maternal HI Titer Related to Characteristics of Infants.

Characteristics	Neg.	1:5	1:15	1:20	1:30	1:40	1:60	1:80	Total
<b>Term Infants</b>									
Normal	45	11	6	21	11	13	2	3	112
Amyotonia (Questionable)	1	0	0	0	0	0	0	0	1
Twins	0	0	0	0	1	0	0	0	1
<b>Total</b>	<b>46</b>	<b>11</b>	<b>6</b>	<b>21</b>	<b>12</b>	<b>13</b>	<b>2</b>	<b>3</b>	<b>114</b>
<b>Prematures</b>									
Normal	2	0	1	2	1	0	0	0	6
Twins	2	0	0	0	0	0	0	0	2
Anencephaly and stillborn	0	1	0	1	0	0	0	0	2
Cleft palate	1	0	0	0	0	0	0	0	1
<b>Total</b>	<b>5</b>	<b>1</b>	<b>1</b>	<b>4</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>12</b>
<b>Total</b>	<b>51</b>	<b>12</b>	<b>7</b>	<b>25</b>	<b>13</b>	<b>13</b>	<b>2</b>	<b>3</b>	<b>126</b>

The cleft palate infant also had a sibling with a cleft palate.

Excluding normal stillbirths and twins in total groups, the incidence of anomalies was 3.0%.

The peak interest in the subject was from 1957-1959. After that time, there have been fewer publications.

Leck, in 1963, summarized the data accumulated, and compared incidence of malformations during the influenza outbreaks in 1957, 1959 and 1961. He stated that the incidence of congenital defects attributed to influenza in the first trimester, as reported by various authors, ranged from 11.6% to 0%. He determined when the peak times of incidence of Asian influenza occurred by inspection of new claims to sickness benefit received weekly by the Ministry of Pensions and National Insurance. He concluded that:

1. There was an increased incidence of esophageal atresia, cleft lip, anal atresia and examphalos.
2. All four above named malformations doubled in incidence following the 1961 epidemic, but only esophageal atresia was common after each epidemic.
3. There was an increased incidence of births with 2 or more of these kinds of defects after each epidemic.

Widelock, Csizmus and Klein, in New York City, published a retrospective study which also extended beyond the 1957 epidemic. They attempted to determine the periods of increased Asian influenza activity. They did this by giving attention to: 1. Mortality data, 2. Frequency of influenza antibodies in various age groups of random samples of population (50 serum samples from each age group tested each month), 3. Virus isolations from throat washings



and autopsy material in order to determine the presence and type of influenza virus in the city during a given period, 4. Influenza antibody determinations on acute and convalescent serum samples submitted by clinicians as corroboration for the existence of Asian influenza infections. By these methods they found the periods of activity to be: 1. October-November 1957, 2. January 15- March 15 1958, 3. December 1958- January 1959, 4. March-April 1959, 5. February-March 1960 and, 6. March 1961. As a result, they came to the following conclusions:

- A. Younger age group maintained higher levels between outbreaks than older individuals.
- B. There was no increase in incidence of prematurity during outbreaks.
- C. There was no increase in incidence of fetal deaths during outbreaks.

Regarding malformations, stillbirths, and neonatal deaths, see Table III.

TABLE III

Relation of Antibody Titers to Malformations,  
Stillbirths and Neonatal Deaths

Malformations	No.	Percent of Total
No increase in titer- Less than 1:64	19	2.836
Four-fold increase	1	.714
No increase in titer- Greater than 1:64	13	2.309
<b>Stillbirths</b>		
No increase in titer- Less than 1:64	15	2.24
Four-fold increase	4	2.857
No increase in titer- Greater than 1:64	12	2.131
<b>Neonatal Deaths</b>		
No increase in titer- Less than 1:64	5	0.746
Four-fold increase	2	1.43
No increase in titer- Greater than 1:64	11	1.954

In Nicaragua, Gallegos and Aguilar found two abortions and three premature births in five women who had been infected with Asian influenza in the first trimester. Hirvensolo and Kinnuner, in Finland, reported that the total incidence and frequency of severe fetal anomalies, number of premature births, stillbirth rate, and perinatal mortality significantly high if the mother was infected with Asian influenza, especially during the first trimester. Both of these authors based their findings on a history of influenza. No antibody titers were done on the mothers.

#### ANIMAL EXPERIMENTATION WITH REGARD TO TERATOGENIC EFFECTS OF ASIAN INFLUENZA

Adams, Heath, Imagawa, Jones and Shear conducted experiments with swiss albino mice and embryonated hens eggs to determine the effect of influenza on the offspring. The experiment was divided into three parts. In part one, twenty mice were bred after intranasal inoculation with sublethal doses of Type A influenza virus. The animals were killed after eighteen days gestation. In part two, fourteen mice were inoculated four days after mating. Part three consisted of neutralizing the effects of the virus with varying dilutions of antiserum before gestation and at different stages of gestation in the chicken embryos. Their results were as follows:

##### A. Mice bred after inoculation

1. Infected mice - 168 live embryos and 10 dead embryos

2. Control mice - 190 live embryos and 5 dead embryos
- B. Mice bred before inoculation
1. Infected mice - 30 subnormal fetuses or implantations sites and 114 normal embryos
  2. Control mice - 17 abnormal fetuses and 130 normal fetuses
- C. Protection of chicken embryos with antiserum - Dilutions of antiserum as high as 1:800 completely protected all embryo against both teratogenic and lethal effects following injection of the mixture with the virus in vitro. Optimum protection was obtained when antiserum was administered before virus inoculation.

#### OTHER FACTORS IN RELATION TO CONGENITAL DEFECTS

The overall incidence of congenital defects in the general population has not been firmly established. One of the most complete studies regarding this was the Fetal Life Study done over a period of ten years at the Sloane Obstetrical Clinic of Columbia-Presbyterian Medical Center. They found a 3.5% incidence of congenital malformations at birth. It was also pointed out in the Life Study that only 50.3% of anomalies are recognized at birth.

Influenza is one of the most difficult diseases to diagnose clinically.<sup>16</sup> Wilson et. al. in Los Angeles showed that even physician-diagnosed influenza was unreliable in determining if the mother actually had influenza. Other viruses, such as the adenoviruses can produce very similar symptoms. Virologists feel that the only certain way to diagnose influenza is to take two blood samples, one in the acute phase and the other 10-14 days later.

There is individual variation in antibody production. However, antibody titer to influenza is usually maximal in 10-14 days with a slow decline thereafter. Most people will continue to have a low titer the rest of their lives.<sup>26</sup>

The type of laboratory test used in the detection of influenza is also important. The hemagglutination-inhibiting test is not specific for influenza. It tests only for the V antigen which is present in all myxoviruses. The complement-fixation test, by Henle, is now considered by some to be more specific.<sup>26</sup>

Lastly, from the virological standpoint, the mode of transmission of the influenza virus from mother to fetus has not yet been determined.<sup>8, 26</sup> Antibodies, as detected by hemagglutination-inhibition, have been found in maternal blood, amniotic fluid and umbilical cord blood. The virus has been isolated from the spleen, liver and kidney in man and in the blood of mice.<sup>8</sup> However, no one, as yet has isolated the influenza virus in the blood stream of man.<sup>8,26</sup>

Epidemiologically, attempts were made by several people to look into other factors that were operating at the same time during a woman's pregnancy that might bias the probability of her child being born with an anomaly.

Acheson suggested that malnutrition plays a part in the causation of anencephaly. He felt that this factor influenced Coffee and Jessop's findings in Dublin.

Peydell found a higher incidence of abnormalities in urban areas,

particularly in industrial belts.

McIntosh, Merritt, Richards, Samuels and Fellows in a five year study, with six and twelve month follow-ups, found that males and non-whites were more prone to congenital abnormalities.

Hewitt studied data from birth and fetal death registrations in New York City (registration of any product of conception is required by law) to identify short periods in which the risks of malformation or death were high or low. He found increased mortality from February through June and in October. The lowest incidence of fetal mortality was in December.

## SUMMARY

Influenza is a very old disease but interest in its effects on fetal development has only been the result of observations made in comparatively recent years. People all over the world have now studied the subject. Their findings are varied.

In the British Isles, Campbell and Belf concluded that there was no increase in abnormalities. Doll, Hill and Sakula found an incidence of 4% abnormalities in the children of 49 patients who had had influenza which was confirmed by a doctor. These mothers had had influenza at least three weeks before their pregnancy. Coffee and Jessop found a 3.5% incidence of defects in the influenza group versus 1.5% in the control group in their prospective study. When the mother was infected in the first trimester, the incidence rose to 7.4%. Three years later in their follow-up study, they reported a 15% and 10% incidence, respectively. There was an increase in central nervous system defects in the influenza group.

In Nicaragua and Finland, two doctors reported an increase in abnormalities. However, in abstracts of their work, none of the data regarding how the research was conducted was included.

The Iowa and Los Angeles groups in American used hemagglutination-inhibition and neutralizing antibody tests to determine whether each mother had had influenza. The Iowa group reported an incidence of 3.3% abnormalities in their patients which included only one mother who had been ill in the first trimester. All of the patients,

including their controls, had positive serum reactions if tested against many strains of the Asian influenza virus. The Los Angeles group tried to correlate titers with influenza and anomalies. They reported an incidence of 3.0% anomalies when the mother said she had influenza at some time during her pregnancy. But, they showed only a chance relationship in defects to increased antibody titers.

The incidence of congenital defects in the general population is thought to be approximately 3.5% at birth. Fifty percent more are discovered after birth.

Virologists feel that two blood samples must be taken to determine the presence of influenza antibodies and that the complement-fixation test, by Henle, is a more specific test. Because influenza viremia has not been proven in man, the method by which the virus may infect the fetus is still being investigated.

Various people have searched for other contributing factors in the causation of defects. Topics discussed were malnutrition, geography, sex incidence and temporal relationships.

Animal experiments with mice and chickens showed a definite increase in abnormalities when the animal had been infected with influenza.



## DISCUSSION

Although there is abundant literature on this subject, most of it is ambiguous, confusing and inconclusive.

First of all, the diagnosis and incidence of congenital abnormalities still needs further study. As pointed out by the Fetal Life Study, only 50% of the abnormalities are diagnosed at birth. Coffee and Jessop were the only ones who did follow-up work. Stillborns and abortions are not as carefully studied as they should be. Edith Potter says that many miscarriages are due to malformations. Drs. Arthur Hertig and John Rock studied eight pre-implantation embryos and found that half were so abnormal that they would have died in a short time if they had not been removed surgically. If this can be applied to all developing embryos, several million more pregnancies are commenced each year than anyone at present suspects, all of which terminate early because of abnormal development.

It is well known that in embryonic development all organs are formed in the first trimester.<sup>26</sup> Therefore, all major congenital anomalies would be incurred during that time. Many authors based their conclusions on data obtained about influenza during the entire pregnancy.

In regard to what constitutes an anomaly, there was disagreement. Some considered only major defects such as anencephaly, cleft palate, congenital heart defects, etc. Others included minor anomalies such as blocked tear ducts and nevi. Each author clarified what he

considered defects within his own report but the variance in opinion made it difficult to assess and compare data from numerous reports.

Lastly, the diagnosis of influenza must be perfected and ancillary factors more closely controlled before further intelligent studies can be done.

## CONCLUSIONS

Some authors write that there is an increased incidence of congenital defects in children of mothers who had contacted influenza during their pregnancy, especially in the first trimester. None of these authors took any blood samples to confirm the diagnosis of influenza.

Those authors who took one blood sample did not find an increased incidence of defects. They, however, neglected to take two blood samples as suggested by virologists.

Because animal experiments showed that influenza is capable of producing teratogenic effects in chicken and mice offspring, the possibility still remains that influenza may be able to produce anomalies in humans.

Influenza is very common in the general population and the pregnant woman runs a high risk of contacting the disease. There is a definite need for further research on this subject. In order that better or more supportable conclusions can be made, future studies should give more attention to the following points:

1. Accurate diagnosis of influenza utilizing laboratory tests.
2. Long range follow-ups.
3. Emphasis on the effects of influenza when contacted in the first trimester.
4. Other factors besides the influenza virus that may be causes of defects.
5. Determination of the route of transmission of the influenza virus from the mother to the fetus.
6. Standardization of the definition of a congenital defect.

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