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Treatment of Newborns and Infants in Japan suffering from Pneumonia with New Antibiotics

by

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Abstract

Despite the recent development of a high state of chemotherapy in Japan, there has not necessarily been an improvement in the prognosis of pneumonia in infants and newborns.

Upon bacteriological examination, relevant causative organisms such as pathogenic staphylococci, pneumococci, streptococci, and gram-negative bacteria have been detected as causing mixed infection.

Suitable chemotherapeutic agents which diffuse well to the lung and show high bactericidal action against such organisms must be selected to combat the infection.

A combination of two synthetic penicillins, ampicillin, effective against gram-negative as well as gram-positive bacteria and cloxacillin effective against resistant staphylococci, was used for the treatment of many cases of pneumonia in infants and newborns and satisfactory results were obtained.

The results of this study and an appraisal of penicillin combination therapy will be discussed.

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Prognosis of newborns and infants suffering from pneumonia in Japan has not significantly improved despite the development of new antibiotics.

This is attributed to various factors including the low natural defense in the young, their greater susceptibility to virus infections, and increasing drug resistance of causative organisms.

I wish to report here on the prognosis of premature and newborn babies suffering from pneumonia who were treated at universities and other large hospitals in Japan. The main causative organisms involved in pneumonia among the young are listed in table 2.

Of late, there has been an increase in complicating infections due to Haemophilus, Escheria coli and other gram-negative bacteria (GNB), in addition to pathogenic Staphylococcus, pneumococcus and beta-Streptococcus. It is therefore necessary to give preference to certain antibiotics having the following descriptions:

1. Broad spectrum antibiotics effective against cocci and bacilli, including Staphylococcus and GNB which have little or no sensitivity to antibiotics.

2. Bactericidal antibiotics.

3. Antibiotics which feature high concentrations in the blood and other body fluids and in various organs, resulting in a strong antibacterial effect.

4. Antibiotics which feature few side-effects when administered to children, even parenterally.

The following antibiotics now used in Japan meet these requirements:

1. Synthetic penicillins and their combined preparations.
2. Aminoglycoside antibiotics (Kanamycin, Kanendomycin, etc.).
3. Cephalosporins (CP).

Many pathogenic Staphylococci isolated in Japan have of late been found resistant to Penicilline G (Pc.G), Tetracycline (TC), Streptomycine (SM) and CP.

We made a study of the prognosis of pneumonia among newborn and premature babies treated at childrens' hospitals in Tokyo with Cloxacillin (MCI-Pc) or Oxacillin (MPI-Pc) both of which are synthetic PCs and effective against resistant Staphylococci. These were compared with prognosis of similar cases treated with conventional antibiotics. Prognosis of group treated with synthetic PCs effective against resistant Staphylococci was found to be superior. (Table 3 dan 4).

Then Viccillin S, a combination of Cloxacillin and Ampicillin, which is effective against GNB, became available, and we began to use it exclusively (Table 5). The reasons for this are as follows:

1. The antimicrobial spectrum of the two antibiotics forming the Viccillin S combination is broadened through synergistic action, and therefore the combination is effective against almost all cocci and GNB.

2. Antibacterial effect after injection is good because satisfactory levels of concentration are attained.

3. It is possible to commence treatment before the causative organisms are identified due to the broadened spectrum of this combination, which is especially helpful in the case of pneumonia in infancy where early treatment is of great importance.

We have treated many cases of pneumonia in infancy using Viccillin S as the main antibiotic. I will report here on part of the results.

A daily dosage of 100 to 250 mg/kg was injected in two or three divided doses for 7 to 10 or more consecutive days. This treatment was effective in 88% of the 54 cases involved. Severe side-effects of synthetic penicillin in young children are very rare, and in our study no side-effects were observed. However, a test for hypersensitive reaction to penicillin is advisable prior to administration.

Kanendomycin, an aminoglycoside antibiotic recently developed in Japan, is now also being used to treat pneumonia in infants. Produced by a mutant strain of Streptomyces kanamyceticus, it has a greater inhibitory effect than Kanamycin against Staph. or E. coli which are resistant to many other antibiotics. Distribution of this antibiotic to the organs after injection was very good. Its MIC against recently isolated Staphylococcus was 0.39 to 0.78 mcg/ml and against E. coli 0.78 to 3.12 mcg/ml. Its mean blood levels were 34.8 mcg/ml at one hour, 28.2 at three hours, 27.9 at six hours and 9.8 at twelve hours after intramuscular injection of 10 mg/kg to newborn babies.

Administration of 5 to 15 mg/kg per day for periods of 7 to 10 days was clinically effective against Staphylococcal pneumonia in almost all cases. No 8th cranial nerve or kidney disorders were observed when administration lasted less than two weeks.

Finally, I would like to show you the results of cases of pneumonia in infants treated at a Japanese university with various antibiotics. (Table 1). It can be seen that synthetic penicillin demonstrated the greatest effectiveness.

TABLE 1 : *Results of Infantile pneumonia treated with various antibiotics (1957 - 1966).*

Antibiotic	Synthetic Pc.	KM	KM + Pc. G.	CER CET	EM	TC	CP	Others
No. of cases	11	18	13	14	6	20	49	18
Effective rate (%)	91.0	77.8	77	71.4	66.6	60	55	44.5

TABLE 2 : *Causative Organisms of pneumonia in infancy (Nov. 1957-Dec. 1965).*

(No. of cases)	Beta-Strept.	Coag(+) Staph.	Pneumo-cocci	Haemoph. Inf.	Gram(—) Bacilli	Pseud.	Proteus
166	13 (7.8%)	62 (37.2%)	23 (13.8%)	15 (9.0%)	32 (19.2%)	13 (7.8%)	4 (2.4%)

FIG. 4 : *Platelets and hematocrit levels in relation to shock and antibody rise.*

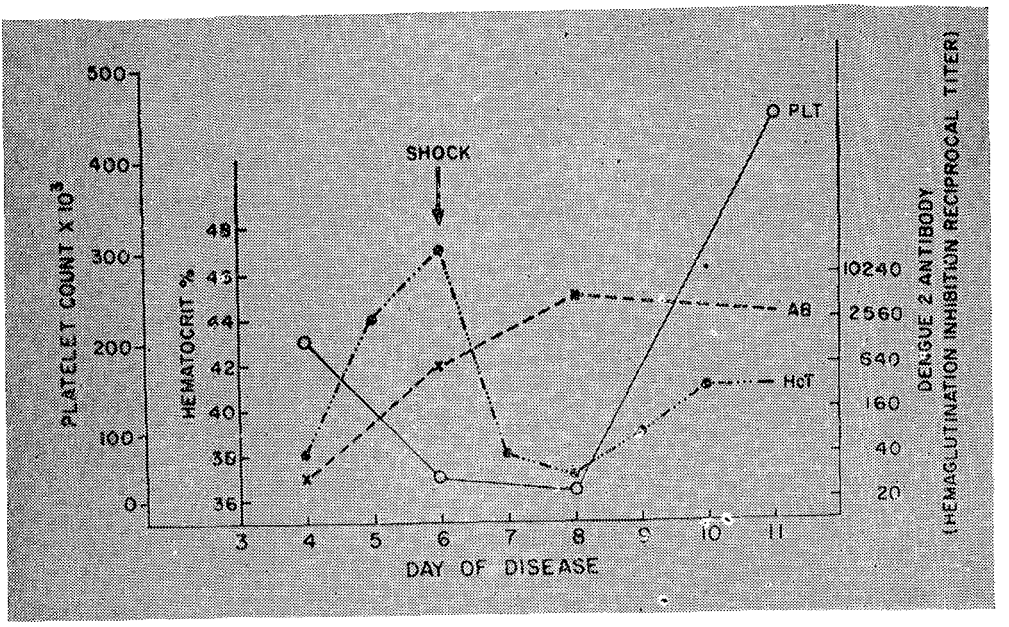

FIG 5 : *The Complement profiles of DHF (W.H.O. 1973).*

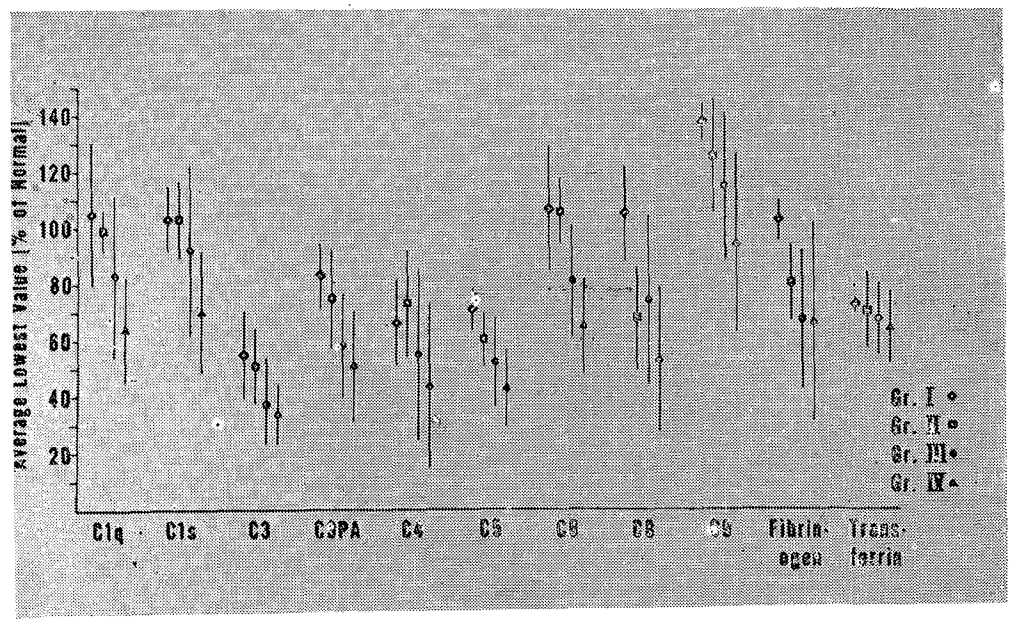

FIG. 6 : *DHF hospitalized cases and deaths, Children's Hospital, Bangkok*

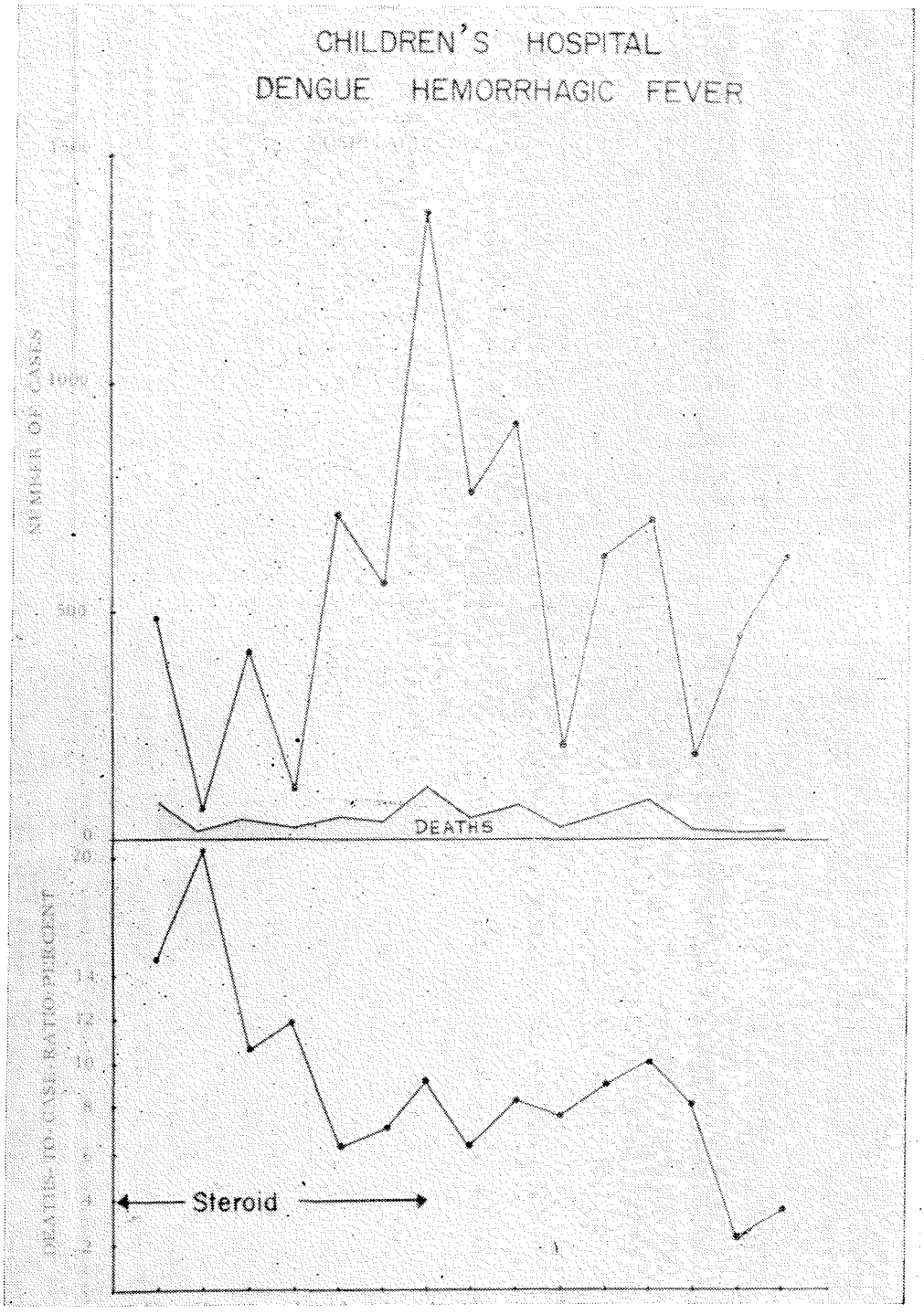

Table 3. Summary of Clinical and Laboratory Findings in 82 Secondary Patients

Findings	UF* (2)**	Dengue Hemorrhagic Fever			
		Gr I (14)	Gr II (38)	Gr III (22)	Gr IV (6)
Fever	2/2 (100)****	14/14 (100)	38/38 (100)	22/22 (100)	6/6 (100)
Hepatomegaly***	1/2 (50)	6/11 (56)	15/30 (50)	16/19 (84)	5/5 (100)
Positive tourniquet test	0/2 (0)	12/13 (92)	36/36 (100)	22/22 (100)	6/6 (100)
Petechiae	0/2 (0)	0/13 (0)	29/36 (81)	16/22 (73)	4/6 (67)
Other signs of bleeding	0/2 (0)	0/13 (0)	14/36 (39)	7/22 (32)	5/6 (83)
Homoconcentration ≥ 20% ↑	0/2 (0)	7/11 (54)	18/36 (50)	18/19 (95)	6/6 (100)
Platelet counts ≤50,000	0/2 (0)	8/14 (57)	24/38 (63)	21/22 (95)	6/6 (100)

* UF indicates undifferentiated fever
** Number of Patients
*** ≥ 2 cm below costal margin
**** Percentage of cases

TABLE 2 : *Clotting studies in dengue hemorrhagic fever*

Test	Result V.S. Disease Severity			
	gr I (5)	gr II (14)	gr III (22)	gr IV (12)
Fibrinogen gm/Lt average minimum level (Control 1.72 gm/Lt)	1.51	1.20	0.98	0.89
Fibrinogen degradation product (percent present)	37.0	41.0	51.0	53.0
The average amount of split products (mg/100 ml).	1.7	3.2	2.9	5.1
Platelet counts (average lowest counts)	59,00	49,000	24,000	20,000

WHO Bulletin, 1973, 48.

viral proteins. The amount of antigen sharing, however, is not sufficient to provide cross protection, thus infection with one sero-type may be followed by infection with a heterologous serotypes (Sabin, 1952; Whitehead et al., 1970).

The virus associated with DHF includes all four serotypes of dengue viruses. An intriguing paradox exists in view of the fact that these same also cause classical dengue fever and benign undifferentiated febrile illness in some endemic and epidemic situations. There are no demonstrable major antigenic differences between dengue strains of the same serotypes causing mild dengue illness and severe DHF (Russell and Nisalak, 1967); each of the four serotypes is capable of producing benign or severe diseases, depending on the epidemic situations.

Extensive epidemiological studies have convincingly demonstrated that DHF occurs where two or more dengue serotypes are simultaneously endemic or sequentially epidemics and where ecological conditions favor efficient virus transmission by the vector mosquitoes. As man is the only significant dengue host and Ae. aegypti the important vector, both the ecological conditions of man and mosquitoes are basic ingredients for DHF outbreak.

Serological studies revealed the association of DHF and DSS with the secondary type antibody response. Fig. 1 shows the age distribution curve of DHF patients admitted to the Children's Hospital, Bangkok, during the 1962 - 1964 outbreaks. There were two modal ages, less than one year and 4 years old; 86% of these were children with secondary dengue infection whose age grouped around the mode of 4 years. The rest were those with primary infection predominantly infants under one year old (Fig. 2). The incidence of shock in the group with secondary antibody response of 40% is significantly different from 8% observed in the group with primary infection.

These epidemiological and serologic observations implicating "the two infection hypothesis" of the pathogenesis of DHF. It has been postulated that during a secondary infection with a dengue virus different from the one that caused the primary infection, an enhanced immunological response plays a central role in disease pathogenesis, through a mechanism which has not been clearly demonstrated (Halstead et al., 1967). The incidence of shock in primary infection, however, remains an enigma. It is likely that in infants under one year of age, passive immunity antidengue IgG antibody from mother, at very low titer is capable of enhancing the immunological sequence as in secondary infection.

It is of interest to note that in Thailand, dengue 2 viruses have been isolated in higher frequency than

other serotypes from cases with secondary antibody response while the proportion of dengue 1, 2 and 3 viruses recovered from mosquitoes and patients with primary dengue infection were nearly equal (Halstead et al., 1970). These observations raised the major question related to correlation of disease severity and the infecting dengue serotypes.

The basic epidemiological conditions essential to the occurrence of DHF appear to be the presence of two or more dengue virus serotypes and a high rate of transmission. The interval between sequential infections may be also an important factor. The fact that no DHF or DSS was observed in Puerto Rico, where two sequential epidemics of dengue occurred in 1963 and 1969 with dengue 3 and dengue 2 respectivelly, suggest that two infections six years apart produce different results than two infections at a shorter interval (within 5 years) as observed in Thailand (Winter et al., 1969; Fischer and Halstead, 1970).

Clinical Aspect

The clinical spectrum of DHF ranges from mild dengue fever like, to the life threatening illness with shock. (Fig. 3). In typical cases, the disease is characterized by four major manifestations, high fever, various hemorrhagic diathesis most commonly skin hemorrhages, hepatomegaly and circulatory disturbance in the form of shock severe cases.

The course of a patient with DHF typically consists of an early febrile period lasting from two to seven days. Anorexia and vomiting are common findings which may contribute to some fluid and electrolyte disturbance.

Hemorrhagic diathesis, most commonly as skin hemorrhage: positive tourniquet test, petechial rash are seen frequently in the early phase of illness. Hemorrhages sometimes may be severe and even fatal; gastrointestinal bleedings as hematemesis and/or melena, when present, often occurs after the onset of shock, more often after prolonged uncontrolled shock.

Hepatomegaly — Enlargement of the liver occurs frequently. The liver may be palpable early in the febrile phase or appears later when the patient became afebrile. A big tender liver is common but jaundice is not usually found.

In a severe case, following fever of a few days duration the patients condition suddenly deteriorates. Accompanying or shortly after the fall in temperature at the end of febrile period, there are signs of circulatory failure; the skin becomes cool, blotchy and congested, circumoral cyanosis is frequently observed and the pulse becomes rapid. Although in some cases they may appear lethargic, patients become restless and then rapidly go into a critical stage of shock. Abdominal pain is a frequent

TABLE 3 : *Prognosis of pneumonia in newborn and premature babies (1957 - 1967).*

(Total: 213 cases)

Institutes	Newborn		Premature	
	Lived	Died	Lived	Died
Tokyo S University	38 67	29 (43.3%)		2
Tokyo TB University	21 35	14 (40.0%)		1
Aomori H University	5 9	4 (44.4%)		
Tokyo E Hospital	41 48	7 (12.5%)		1
Tokyo Mother & Children Hospital	31 38	7 (18.4%)	8 12	4 (33.3%)
Total	197	(31.5%)	16	(50.0%)

(Author's findings)

TABLE 4 : *Prognosis of pneumonia in newborn and premature babies in accordonce with antibiotic used (Mother & children Health Care Center of Tokyo : 19 Cases).*

Antibiotics & administration methods	Newborn		Premature	
	Lived	Died	Lived	Died
CP, TC, PC Injection or Oral	15 (71.4%)	6 (28.6%)	4 (57.0%)	3 (13%)
Cloxacillin Injection	16 (94.1%)	1 (5.9%)	4 (100%)	0 (0)

(Author s findings)

Chronological changes in death rate of newborns, infants and children. (Deaths in 1950 = 100).

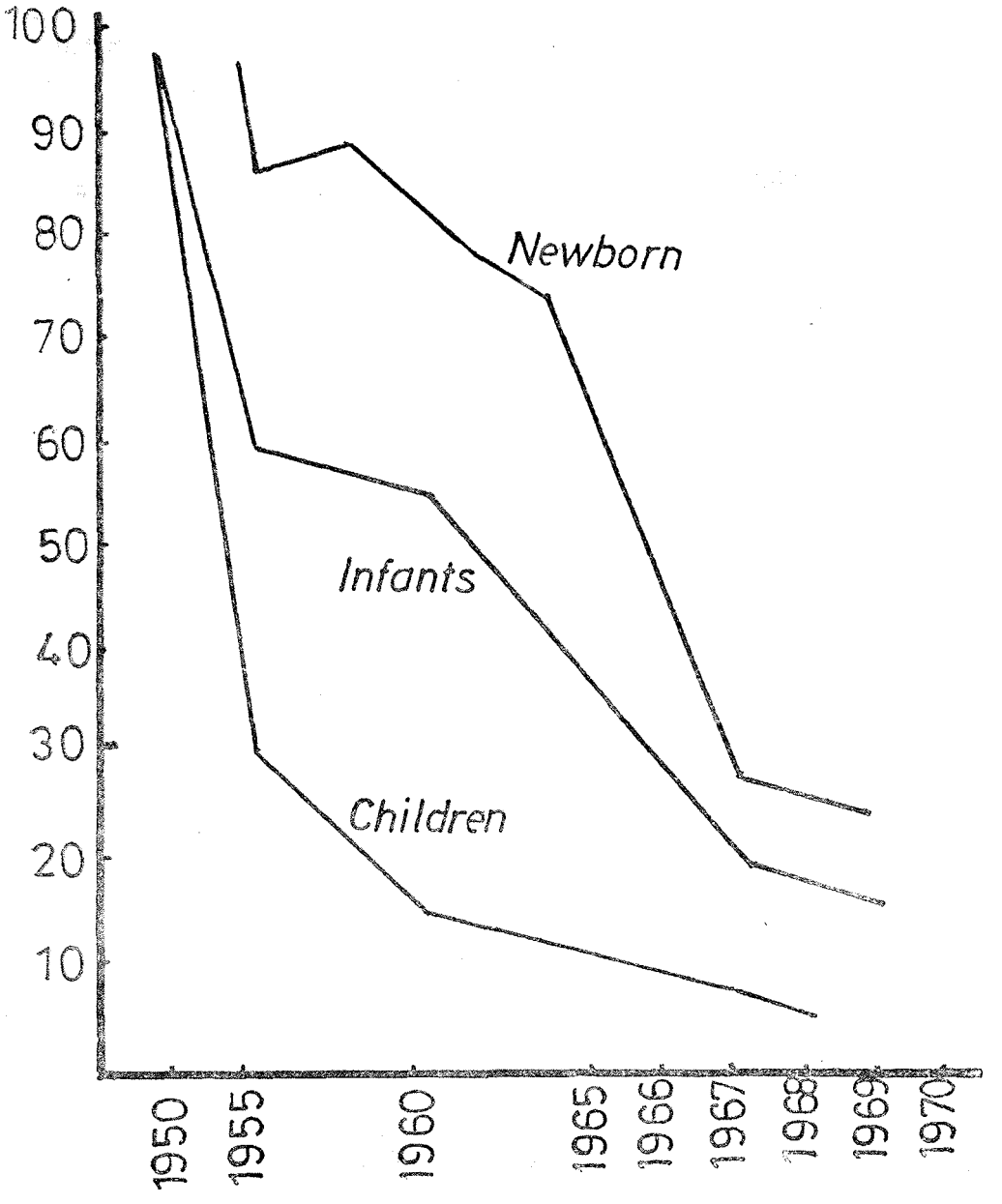

TABLE 6 : *Effectiveness of Vicillins S against Pneumonia in newborn and infants.*

Cases	Vicillin S injections			Prognosis	
	One dose (mg)	Daily dosage (mg)	Duration	Lived	Died
54	100 - 250	200 - 750	7 - 15 days	48	6
				Effectiveness 88%	

TABLE 7 : *Drug Resistance of Staphylococcus aureus in Japan (1965 ..... 3844 Strains).*

(Antibiotics)	(Resistant strains)
SA	86 %
PcG	69.1%
SM	28.7%
TC	34.9%
CP	15.4%
EM	20.5%
NB	5.5%
DMP	2.1%
KM	4.7%