Application of Antibiotics to Livestock and Its Problems

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Antibiotics with contribute to stock-raising

Today the world population, which grows yearly by 2 per cent, has increased enormously, reaching 3.7 billion, but about half of the population is found in the starvation or chronic malnutrition condition. According to the warning of the Food and Agriculture Organization of the United Nations, the number of persons who died of starvation reaches 10 thousand every day, resulting in 3 million dead annually, while it is estimated that the increasing rate of producing general food is 1.8 per cent per year. It must be said that the future of the human being is in a precarious condition, if it would undergo a transition under such food conditions.

Some 2,400 calories containing a protein of 70 grams daily, in which an animal proteid of at least 20 grams should be included, are required for man to lead an active and healthful life.

According to statistics, an animal proteid of 66 grams per person per day is the intake in North America, 62 grams in Oceania and 33 grams in Western Europe. Thus, such rich meals are taken in some countries, while it is said that in other regions which are occupied by most of the world population, such as the Middle East, Near East, Africa and Asia, the intake is 14 grams, 11 grams and 8 grams respectively. Some way should be devised so that these people, who are not blessed with animal proteid, could partake 20 grams every day which is considered to be the minimum required amount.

If the whole amount is not always supplied by livestock products, a supreme effort must be made scientifically and technically to increase the productivity of food, especially animal proteid which is the root of bringing peace and happiness of the human being.

Antibiotics which have greatly contributed in saving human being from the curse of diseases and maintaining their lives, have also shown to livestock the similar mercy. They have surprisingly increased the productivity of livestock, and also from the viewpoint of enhancement of livestock products. They have played an unexpectedly important role not only in saving them from diseases but also in promoting their growth, etc.

The productivity which could be obtained by the new livestock management of today is much higher than that of the old one. Especially it is conspicuous in the stock-raising of medium and small animals, above all in case of broiler and swine raising.

It has been proved that the productivity, which is considered to be natural these days, has made great progress, if compared with that in times when excellent medical supplies such as antibiotics were not developed.

The efficacy of antibiotics in the livestock industry is remarkable; it not only improves the growing speed and the size of living body but also increases the number of animals in definite space of establishment, promotes labor-saving of breeding management and increases the rotation of

production by reducing the breeding period. Additionally it has been helpful in increasing the economical value by making the size of carcass produced uniform. Thus, the amount used and the kind of antibiotics for livestock use have greatly increased yearly in Japan.

Consumption amount of antibiotics for animal

Today many kinds of antibiotics are used for chemothrapentic purpose. However the kinds which are used to prepare drugs for animal are comparatively small. For example, about 30 kinds of antibiotics were used in 1971, as shown in Table 1 (the names of antibiotics will be abbreviated as the ones described respectively in this table). As for the amount used, the antibiotics which have been used in large quantities are restricted, as shown in Table 2. Quoting the figure from Table 2, 18 trillion units of penicillin have been used in 1971, most of which is procaine penicillin G. This is very different from the fact that many kinds of synthetic penicillin are used for human chemotherapy.

If the weight of 1,000 units of procaine penicillin G is 1 mg for convenience, the weight of 18 trillion units of the consumed penicillin is about 18 tons, which is equivalent to 7.6 per cent of the total amount of antibiotics used for animal in the concerned year of 237,064 kg.

Antibiotics of tetracycline series used for livestock in Japan consist of three kinds—OTC, CTC and TC. The amount used of OTC is 36,101 kg, CTC is 39,546 kg, and TC is 1,069 kg, of which the total is 76,716 kg and is equivalent to about 32 per cent of the total amount of antibiotics used in the concerned year.

Antibiotics of streptomycin series used for animal are SM and DSM. The amount used of SM is 4,136 kg, DSM is 5,295 kg of which the total is 9,430 kg and is equivalent to 3.9 per cent of the total amount.

Table 1. Antibiotics used for veterinary purpose in Japan

Group of antibiotics	Antibiotic	Short for antibiotic
Penicillins	Benzyl penicillin	PC-G
	Methyl chlorophenyl isoxazolyl penicillin	CX
Tetracyclines	Tetracycline	TC
	Oxytetracycline	OTC
	Chlortetracycline	CTC
	Pyrrolidinomethyltetracycline	PTC
Aminoglycosidic antibiotics	Streptomycin	SM
	Dihydrostreptomycin	DSM
	Dihydrodesoxystreptomycin	DOS
	Fradiomycin	FM
	Kanamycin	KM
	*Hygromycin-B	HM
	*Destomycin-A	DM
	*Kasugamycin	KSM
Peptide antibiotics	Polymyxin-B	PM
	Colistin	CL
	Mikamycin	MK
	Bacitracin	BC
	*Virginiamycin	VM
	*Thiopeptin	TP
Macrolide antibiotics	Oleandomycin	OM
	Erythromycin	EM
	Leucomycin	LM
	*Tylosin	TS
	Spiramycin	SP
Chloramphenicols	Chloramphenicol	CP
	Chloramphenicol palmitate	CPP
Others	Novobiocin	NB
	Macarbomycin	MC

Note: * Antibiotic not used for human

Amynoglycosidic antibiotics used for veterinary purpose consist of six kinds, including SM and DSM and others such as FM, KM, DM and HM. The consumption amount of the latter four antibiotics is respectively 8,744 kg, 14,053 kg, 7,714 kg and 1,798kg. The total amount used of these six kinds of aminoglycosidic antibiotics is 41,839 kg of which the proportion is as large as 17.6 per cent.

Among antibiotics of macrolide series the

Table 2. Animal-use antibiotics consumed in fiscal year 1971 (In terms of net powder weight)

Antibiotics	Feed additives (g)	Oral preparations (g)	Injections (g)	Insertions (g)	Infusions (g)	Total (g)	%
1 Penicillins	**4,883,725**	**8,118**	**12,475,472**	**21,128**	**583,333**	**17,971,776**	
1 PC	4,883,725	8,118	12,475,472	21,128	573,397	17,961,840	7.57
2 CX					9,936	9,936	
2 Tetracyclins	**59,376,132**	**16,202,542**	**1,010,878**	**40,847**	**94,650**	**76,716,049**	**32.35**
1 TC		1,064,125	5,119			1,069,244	0.45
2 CTC	31,818,028	7,685,856		39,999	2,380	39,546,263	16.68
3 OTC	27,549,104	7,452,561	1,005,759	848	92,270	36,100,542	15.22
3 Aminoglycosidic antibiotics	**34,149,380**	**1,767,428**	**5,033,689**	**15,783**	**772,918**	**41,739,198**	**17.57**
1 SM	2,410,800	1,725,270				4,136,070	1.74
2 DSM		24,135	4,692,279	15,783	562,532	5,294,729	2.23
3 FM	8,579,344				164,481	8,743,825	3.68
4 KM	13,647,615	18,023	341,410		45,905	14,052,953	5.92
5 HM	1,797,821					1,797,821	0.75
6 DM	7,713,800					7,713,800	3.25
4 Peptide Antibiotics	**41,369,081**	**226,400**	**281**		**316**	**41,596,078**	**17.52**
1 PM					316	316	
2 CL	3,815,342		281			3,815,623	1.60
3 MK	476,379					476,379	0.2
4 BC	36,893,010	226,400				37,119,410	15.65
5 VM							
6 TP	184,350					184,350	0.07
5 Macrolide antibiotics	**42,948,861**	**6,517,510**	**3,444,658**		**43,423**	**52,954,452**	**22.31**
1 OM	747,021	128,295	2,544		15,597	893,457	0.37
2 EM		457,684	416,300			873,984	0.36
3 LM	4,068,868	241,470	229,625		20,126	4,560,089	1.92
4 TS	27,594,388	3,703,336	890,489			32,188,213	13.57
5 SP	10,538,584	1,986,725	1,905,700		7,700	14,438,709	6.09
6 Chloramphenicol	**749,675**	**4,210,455**	**806,012**		**27,596**	**5,793,738**	**2.44**
CP	749,675	4,210,455	806,012		27,596	5,793,738	2.44
7 Others	**290,475**	**2,000**			**475**	**292,950**	
1 MC	290,475					290,475	0.12
2 NB		2,000			475	2,475	
Total	**183,758,329**	**28,934,453**	**22,770,990**	**77,758**	**1,522,711**	**237,064,241**	
%	77.51	12.20	9.6	0.03	0.64	100	

amount used of TS is 32,188 kg, SP is 14,439 kg, LM is 4,560 kg, OM is 893 kg and EM is 874 kilograms, of which the total is 52,954 kg and occupies a large proportion of 22.3 per cent of the total amount.

The consumed amount of BC is 37,119 kg and it is the biggest figure among the antibiotics of peptide series. The quantity of the antibiotics included in this series is as follows: CL is 3,816 kg, MK is 476 kg, TP is 184 kg and PM is 0.3 kilograms. Antibiotics of this group used for animal consist of six kinds, of which the total is 41,596 kg and is equivalent to 17.5 per cent of the total amount, most of which are BC. It is only a short time since CL, MK, TP and VM have been put into practice in veterinary purpose, and the amount used is small.

These antibiotics belonging to the peptide group have such common characteris-

tics that they have specific antibacterial responses. Some of them are used exclusively for animals, and most of them are not easily absorbed from the digestive canal. These special characters of antibiotics will help to eliminate pollution caused by antibiotics for animal.

The amount used for antibiotics as feed additives in fiscal 1971 was 183,758 kg, which is equivalent to over 77.5 per cent of a total amount of antibiotics for animal of 237 tons. The amount of oral preparations to be used orally for chemotherapy is 28,934 kg which occupies 12 per cent of the total amount. Both of these preparations which are used orally for animal aggregated 212,692 kg. and reached about 90 per cent of the total amount.

The amount of antibiotics used in feed additives according to the year is shown in Table 3; it was 75,239 kg in 1966, 96,683 kg in 1967, 149,833 kg in 1968, 158,008 kg in 1969 and 176,506 kg in 1970. Meanwhile the demand has rapidly increased in the past several years.

Similarly the demand for oral preparations has greatly increased as shown in Table 4; it was 1,144 kg in 1966, 20,802 kg in 1967, 28,226 kg in 1968, 36,397 kg in 1969 and 39,240 kg in 1970.

The amount of antibiotics used in preparations of injections is indicated in Table 5; it was 9,552 kg in 1966, 16,993 kg in 1967, 17,920 kg in 1968, 19,157 kg in 1969 and 24,562 kg in 1970, of which the total is equivalent to 10 per cent of the total amount used in the concerned fiscal year.

The consumption amount of antibiotics used as infusions and insertions for chemotherapy of mastitis and uteritis is shown in Tables 6 and 7, of which the total values in both tables have increased; it was 1,122 kg in fiscal 1966, 1,671 kg in 1967, 2,006 kg in 1968, 2,694 kg in 1969, 3,520 kg in 1970 and 1,601 kg in 1971, of which the total is still below 0.6 per cent of the total amount used of antibiotics for animal.

The above-mentioned is the outline of antibiotics used for livestock in Japan, among which are 30 kinds of antibiotics for animal. The two points stressed here are that there are several kinds of antibiotics such as the tetracycline series which are used especially in great quantities. On the other hand, from the viewpoint of the course of application to livestock, those which are used orally by means of adding to feed and drinking water occupy the major part, where the amount reaches 90 per cent of the total amount of antibiotics used for livestock. These facts are considered to be one of the key points in solving the formidable problems which are caused by application of antibiotics for livestock.

Residue of antibiotics in the living body

In order to conduct efficiently not only chemotherapy but also pharmacotherapy, it is important to increase the distribution amount of drug in the living body by activating the absorption of the drug used and to maintain the required concentration as long as possible. However how effective the drug in vitro may be, it is impossible to expect the effect of the drugs which is not absorbed in vivo, or is excreted before it shows the effect, even if it is once absorbed, or if it is completely changed into the heterogeneous substance by decomposing or deactivation rapidly.

Antibiotics itself used for animal are mostly excreted in a short time even if they are once absorbed. All drugs that could be used on the stock-raising management of the day should be productive and of labor-saving. However how effectual it may be, the range of application for animals is extremely restricted, if the direction of drug is too complicated or troublesome.

In such a meaning, from the labor-saving viewpoint, it is desirable that the drug used once is maintained in the body for several hours, days or weeks, and if the required

Table 3. Antibiotics used in feed additives (In terms of net powder weight)

	Fiscal year →	1966		1967		1968		1969		1970		1971	
	Antibiotics	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*
1	Penicillins	**9,960**		**9,558**		**11,812**		**11,573**		**8,775**		**4,884**	
	1 PC	9,960	13.5	9,558	9.5	11,812	8.0	11,573	7.5	8,775	5.0	4,884	2.65
	2 CX												
2	Tetracyclins	**31,442**	**41.8**	**40,742**	**42.2**	**70,715**	**47.5**	**63,790**	**41.3**	**76,923**	**43.6**	**59,376**	**32.3**
	1 TC												
	2 CTC	21,580	28.7	22,562	23.4	48,770	33.0	30,746	19.9	27,767	15.7	31,818	17.3
	3 OTC	9,862	13.1	18,180	18.8	21.945	14.6	33,004	21.4	49,156	27.8	27,549	14.99
3	Aminoglycosidic antibiotics	**30,562**	**42.6**	**33,233**	**34.4**	**42,829**	**28.6**	**45,178**	**29.3**	**44,130**	**25.0**	**34,149**	**18.5**
	1 SM	26,570	37.2	26,043	27.0	31,493	21.0	25,577	16.6	13,427	7.6	2,411	1.31
	2 DSM	32	0.2										
	3 FM			2,050	2.3	4,734	3.2	5,509	3.5	9,889	5.6	8,579	4.66
	4 KM			300		2,000	1.3	5,554	3.6	10,094	5.7	13,648	7.4
	5 HM	3,960	5.6	4,840	5.1	4,312	2.9	2,550	1.7	2,958	1.7	1,798	0.97
	6 DM					290	0.2	5,988	3.9	7,762	4.4	7,714	4.19
4	Peptide antibiotics	**18**		**232**		**1,639**	**1.14**	**6,475**	**4.1**	**14,464**	**8.2**	**41,369**	**22.51**
	1 PM												
	2 CL							177	0.01	977	0.6	3,815	2.07
	3 MK	18	0.02	232	0.2	382	0.3	506	0.3	441	0.2	476	0.25
	4 BC					1,257	0.84	5,792	3.8	13,009	7.4	36,893	20.0
	5 VM									6	0.003		
	6 TP									31	0.02	184	0.1
5	Macrolide antibiotics	**3,258**	**5.8**	**12,841**	**13.4**	**22,526**	**15.0**	**30,784**	**19.9**	**31,320**	**17.6**	**42,949**	**23.33**
	1 OM	328	0.44	2,652	2.8	3,892	2.6	897	0.6	427	0.2	747	0.4
	2 EM												
	3 LM	129	1.7	249	0.3	445	0.3	1,439	0.9	2,029	1.1	4,069	2.2
	4 TS					3,800	2.5	9,888	6.4	15,019	8.5	27,594	15.0
	5 SP	2,801	3.7	9,940	10.4	14,389	9.6	18.560	12.0	13,845	7.8	10,539	5.73
6	Chloramphenicol			**76**		**312**		**208**		**405**		**750**	
	1 CP			76	0.08	312	0.2	208	0.1	405	0.2	750	0.4
7	Others											**290**	
	1 MC											290	
	2 NB												
	Annual total	**75,239**		**96,683**		**149,833**		**158,008**		**176,506**		**183,758**	

* Percentage of total consumption in that year

Table 4. Antibiotics used in oral preparations for animal (In terms of net powder weight)

	Fiscal year →	1966		1967		1968		1969		1970		1971	
	Antibiotics	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*
1	Penicillins									**12**		**8**	
	1 PC									12	0.03	8	0.03
	2 CX												
2	Tetracyclins	**8,299**	**74.5**	**10,290**	**49.6**	**16,694**	**59.4**	**19.746**	**54.2**	**25,034**	**63.8**	**16,203**	**56**
	1 TC	987	8.7	986	4.7	1,286	4.8	1,892	5.2	1,086	2.8	1,064	3.7
	2 CTC	3,481	31.1	4,255	22.0	8,429	29.8	7,232	19.8	9,697	24.7	7,687	26.5
	3 OTC	3,831	34.5	5,049	24.2	6,979	24.8	10,622	29.1	14,251	36.3	7,453	25.7
3	Aminoglycosidic antibiotics	**1,039**		**5,372**		**4,592**		**4,401**		**3,846**		**1,767**	**6.1**
	1 SM	912	8.2	5,348	25.6	4,434	15.7	3,933	10.8	2,106	5.4	1,725	5.9
	2 DSM									43	0.1	24	0.08
	3 FM	127	0.1	19	0.09	121	0.4	458	1.2	1,669	4.3		
	4 KM			5		37	0.1	10	0.02	28	0.07	18	0.06
	5 HM												
	6 DM												
4	Peptide antibiotics	**68**		**91**		**325**		**485**		**1,366**		**226**	
	1 PM												
	2 CL	4											
	3 MK												
	4 BC	64	1.1	91	0.4	325	1.1	485	1.3	1,366	3.5	226	0.78
	5 VM												
	6 TP												
5	Macrolide antibiotics	**1,348**		**2,697**		**4,261**		**5,680**		**4,898**		**6,518**	**22.5**
	1 OM											128	
	2 EM					139	0.49	634	1.7	137	0.3	458	1.6
	3 LM			318	1.58	187	0.7	344	0.9	343	0.9	241	0.8
	4 TS	1,335	11.9	2,077	9.9	1,921	6.8	2,281	6.2	2,417	6.2	3,703	12.8
	5 SP	13		302	1.5	2,014	7.1	2.421	6.6	2,001	5.1	1,987	6.9
6	Chloramphenicol	**391**		**2,350**		**2,354**		**5,890**		**3,773**		**4,210**	
	1 CP	391	3.9	2,350	11.3	2.354	8.4	5,890	16.1	3,773	9.6	4,210	14.6
7	Others							**196**		**309**		**2**	
	1 MC												
	2 NB							196	0.5	309	0.8	2	0.007
	Annual total	**11,114**		**20,802**		**28,226**		**36,397**		**39,240**		**28,934**	

* Percentage of total consumption in that year.

Table 5. Antibiotics used in injections for animal (In terms of net powder weight)

	Fiscal year →	1966		1967		1968		1969		1970		1971	
	Antibiotics	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*
1	Penicillins	**7,639**		**9,300**		**9,553**		**10,449**		**13,083**		**12,475**	**54.8**
	1 PC	7,639	79	9,300	54	9,533	53.3	10,449	54.5	13,083	53	12,475	54.8
	2 CX												
2	Tetracyclins	**397**		**555**		**631**		**1,017**		**1,410**		**1,011**	**4.4**
	1 TC									78	0.3	5	0.02
	2 CTC												
	3 OTC	397	4.1	555	3.2	631	3.5	1,017	5.3	1,332	5.4	1,006	4.4
3	Aminoglycosidic antibiotics	**1,478**		**5,934**		**5,647**		**5,487**		**7,349**		**5,034**	**22.1**
	1 SM									4	0.01		
	2 DSM	1,478	15.9	5,934	35	5,596	31.2	5,281	27.5	6,574	27	4,692	20.7
	3 FM												
	4 KM					51	0.28	206	1.0	771	3.1	341	1.5
	5 HM												
	6 DM												
4	Peptide antibiotics									**3**		**0.3**	**0.001**
	1 PM												
	2 CL									3	0.01	0.3	0.001
	3 MK												
	4 BC												
	5 VM												
	6 TP												
5	Macrolide antibiotics	**0.6**		**804**		**1,231**		**1,271**		**1,670**		**3,445**	**15.1**
	1 OM									39		2.5	0.01
	2 EM					99	0.55	305	1.5	64	0.2	416	1.8
	3 LM									13	0.05	229	1
	4 TS	0.4		89		366	2.0	51	0.2	487	1.9	891	3.9
	5 SP	0.2		715	4.2	766	4.2	915	4.7	1,067	4.3	1,906	8.4
6	Chloramphenicol	**37**		**400**		**859**		**788**		**1,045**		**806**	**3.5**
	1 CP	37		400	2.3	859	4.8	788	4.1	1,045	4.2	806	3.5
7	Others												
	1 MC												
	2 NB												
	Annual total	**9,552**		**16,993**		**17,920**		**19,157**		**24,562**		**22,771**	

* Percentage of total consumption in that year

Table 6. Antibiotics used in infusive preparations for animal (In terms of net powder weight)

	Fiscal year →	1966		1967		1968		1969		1970		1971	
	Antibiotics	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*
1	Penicillins	**339**		**404**		**519**		**729**		**960**		**583**	**38.3**
	1 PC	339	32	404	29.9	519	33.6	729	32.0	960	31	573	37.6
	2 CX											10	0.7
2	Tetracyclins	**146**	**13.8**	**174**	**12.7**	**139**	**8.6**	**158**	**6.9**	**190**	**6**	**94**	**6.2**
	1 TC												
	2 CTC	47	4.3	67	4.9	49	3.1	35	1.5	52	1.6	2	0.1
	3 OTC	99	9.4	107	7.9	90	5.5	123	5.4	138	4.0	92	6.0
3	Aminoglycosidic antibiotics	**529**		**707**		**838**		**1,238**		**1,863**		**773**	**50.7**
	1 SM												
	2 DSM	342	32.3	451	33.4	570	34.9	772	33.9	1,021	32	563	36.9
	3 FM	163	15.4	214	15.8	218	13.3	402	17.6	771	24.8	164	10.7
	4 KM	24	2.2	42	3.1	50	3.4	64	2.8	71	2.3	46	3.0
	5 HM												
	6 DM												
4	Peptide antibiotics	**0.63**		**0.95**		**2.6**		**2.9**		**3.02**		**0.3**	**0.01**
	1 PM	0.03		0.05		0.1		0.11	0.005	0.02		0.3	0.01
	2 CL	0.2		0.2		0.5		0.8	0.04	1	0.03		
	3 MK												
	4 BC	0.4		0.7		2		2	0.09	2	0.06		
	5 VM												
	6 TP												
5	Macrolide antibiotics	**20**		**32**		**48**		**82**		**41**		**43**	**27.6**
	1 OM	5		9		11	0.7	19	0.8	9	0.2	16	1.1
	2 EM												
	3 LM	11		17	1.2	24	1.5	48	2.1	27	0.9	20	1.3
	4 TS												
	5 SP	4		6	0.4	13	0.8	15	0.6	5	0.1	7.7	0.5
6	Chloramphenicol	**23**		**33**		**46**		**64**		**47**		**27.6**	**1.8**
	1 CP	23	2.1	33	2.4	46	2.8	64	2.8	47	1.5	27.6	1.8
7	Others	**0.5**		**0.8**		**2**		**2**		**0.3**		**0.5**	**0.03**
	1 MC												
	2 NB	0.5		0.8		2		2	0.09	0.3	0.01	0.5	0.03
	Annual total	**1,057**		**1,351**		**1,594**		**2,276**		**3,106**		**1,523**	

* Percentage of total consumption in that year

Table 7. Antibiotics used in insertions (In terms of net powder weight)

Fiscal year →	1966		1967		1968		1969		1970		1971	
Antibiotics	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*	Consumption (kg)	%*
1 Penicillins	**19**		**30**		**64**		**67**		**29**		**21**	**26.9**
1 PC	19	29	30	9.3	64	15.5	67	16	29	7	21	26.9
2 CX												
2 Tetracyclins	**35**		**265**		**302**		**302**		**361**		**41**	**52.7**
1 TC												
2 CTC	35	53	265	82.8	302	73.3	302	72.2	261	63	39.9	51.3
3 OTC									100	24.1	0.8	1.0
3 Aminoglycosidic antibiotics	**12**		**26**		**47**		**50**		**24**		**16**	**20.5**
1 SM												
2 DSM	12	18.4	25	7.8	47	11.4	50	11.9	24	5.7	16	20.5
3 FM			0.8									
4 KM												
5 HM												
6 DM												
4 Peptide antibiotics												
1 PM												
2 CL												
3 MK												
4 BC												
5 VM												
6 TP												
5 Macrolide antibiotics												
1 OM												
2 EM												
3 LM												
4 TS												
5 SP												
6 Chloramphenicol												
1 CP												
7 Others												
1 MC												
2 NB												
Annual total	**65**		**320**		**412**		**418**		**414**		**77.8**	

* Percentage of total consumption in that year

concentration could be maintained in the body until the aim sought is achieved by one administration. Such drug would contribute to the productivity of the livestock industry from the standpoint of labor-saving. Consequently there occurred different views about the merits and demerits of the residue of these antibiotics.

In order to increase the efficiency of chemotherapy and to solve problems on food sanitation, it is important to examine the characteristics of absorption and distribution of antibiotics from the experimental result of some major antibiotics which are consumed in large quantity for livestock and have a long history of application to animal.

1) The distribution of potassium penicillin G in chickens after the intramuscular injection with the dose of 50,000 unit/kg, B.W., is shown in Table 8, where the concentration value is the highest in the bile, but it is extremely lower in the spleen, the testis and the brain, and the level of the rest of the test materials dispersed between the two extreme concentration figures.

The time when the distribution of PC in most of the test materials reaches the highest value is about 10 minutes after injection. It is not determined after 6 to 12 hours in the other tissues except the bile and the kidney.

The distribution value in chickens after the oral administration of penicillin of the same amount as intramuscular injection is shown in Table 9; where the maximum value is seen in the bile, the next high values is seen in the serum and the kidney, and lower concentration is detected in the other organs. The peak levels of penicillin in most of the test materials are accepted from 30 minutes to 1 hour after the oral administration. The concentration in the bile is detectable up to 24 hours after the administration, while it cannot be proved from the other test materials that have passed more than 2 or 6 hours.

These results are similar to those which Ninomiya, et al.[1], have experimented using goats, Ullberg[2] using mice and Fujimoto, et al.[3], using rats, and they all agree to the result that Hirsh[4] has obtained in the experiment of the concentration in human blood.

2) Dihydrostreptomycin

The distribution of DSM in chickens after the intramuscular injection of it with the dose of 100 mg/kg, B.W. is shown in Table 10, where the large values are seen in the

Table 8. Distribution of potassium penicillin G in chickens after intramuscular injection (Ninomiya et al.)

Organ	Time										Cont.
	5 m	10 m	20 m	30 m	1 hr	2 hrs	3 hrs	6 hrs	12 hrs	24 hrs	
Serum	*6.3	17.8	13.6	14.5	4.9	3.4	2.2	0.3	0	0	0
Muscle	1.1	4.6	2.2	1.7	0.5	0.5	0.2	0.1	0	0	0
Lung	5.4	14.5	8.1	7.1	2.7	1.5	0.8	0	0	0	0
Liver	0.8	4.9	3.9	2.0	1.0	0.8	0.2	0	0	0	0
Bile	6.1	40.1	67.5	88.8	291.3	271.3	97.5	123.4	63.8	57.5	0
Spleen	0	1.5	1.9	2.0	0.3	0.3	0.1	0	0	0	0
Pancreas	1.4	1.8	1.3	5.0	0.9	0.9	0.6	0.5	0	0	0
Testis	0.2	1.5	1.3	1.7	1.0	0.7	0.6	0	0	0	0
Kidney	3.8	37.8	14.8	12.1	6.9	3.7	2.5	0.6	0.1	0	0
Heart	3.4	10.1	4.0	3.9	1.8	1.7	1.5	1.1	0	0	0
Brain	0	0.3	0.3	0.3	0.1	0.1	0	0	0	0	0

Note: * Units/g or ml. Dosage: Potassium penicillin G 50,000 units/kg

Table 9. Distribution of potassium penicillin G in chickens after oral administration (Ninomiya et al.)

Organ	Time							Cont.
	10 m	30 m	1 hr	2 hrs	6 hrs	12 hrs	24 hrs	
Serum	*1.36	9.76	1.45	0.18	0	0	0	0
Muscle	0	0.38	0.48	0.39	0	0	0	0
Lung	0	0.33	0.41	0.27	0	0	0	0
Liver	0	0.37	0.20	0	0	0	0	0
Bile	2.10	40.00	32.20	28.80	10.90	2.70	0.75	0
Spleen	0	0	0	0	0	0	0	0
Pancreas	0	0.35	0.38	0	0	0	0	0
Testis	0	0.18	0	0	0	0	0	0
Kidney	0.40	0.58	2.10	0.13	0	0	0	0
Heart**	0.13	0.40	0.47	0	0	0	0	0
Brain	0	0.18	0	0	0	0	0	0
・Corp	1,250.00	762.50	606.30	105.00	8.90	3.60	0.38	0
・Gizzard	6.80	3.80	6.00	1.10	0.24	0.20	0	0
・Small intestine	105.00	637.50	74.20	6.25	1.20	0	0	0
・Cecum	0	0	0	0.15	1.10	0.16	0	0
・Rectum	0	19.30	49.40	589.10	3.70	0	0	0

Note: * Units/g or ml. ** Heart muscles. ・Contents in each type of digestive tract. O:None, or concentrations below demonstrable level. Potassium penicillin G, 50,000 units/10 ml/kg (body weight)

Table 10. Distribution of dihydrostreptomycin sulfate in chickens after intramuscular injection (Ninomiya et al.)

Organ	Time										Cont.
	5 m	10 m	20 m	30 m	1 hr	2 hrs	3 hrs	6 hrs	12 hrs	24 hrs	
Serum	62.4	84.2	98.3	123.3	127.4	83.8	54.6	25.4	16.3	1.4	—
Muscle	0.5	0.9	2.6	2.8	3.2	2.4	1.8	0.5	—	—	—
Lung	14.7	21.6	22.8	23.7	30.0	22.8	15.6	7.5	5.7	1.26	—
Liver	2.8	7.2	9.5	13.8	15.0	14.7	15.0	15.0	18.6	6.6	—
Bile	2.6	3.8	7.2	10.8	27.0	13.2	13.2	15.6	16.2	2.9	—
Spleen	4.3	4.1	5.7	10.8	9.0	6.6	6.0	4.4	5.4	2.6	—
Pancreas	1.2	3.2	3.8	14.7	5.9	4.7	2.6	0.7	0.6	—	—
Testis	1.6	2.8	4.8	5.4	13.2	8.7	6.6	4.5	4.0	1.9	—
Kidney	22.9	28.1	34.5	47.4	59.9	56.6	54.0	52.7	61.9	26.0	—
*Heart	6.9	13.2	13.2	16.5	17.4	13.8	9.9	3.6	3.2	—	—
Brain	—	1.2	1.3	1.4	3.2	1.5	1.4	1.1	1.1	0.5	—

Note: DSM 100 mg/kg B. W. *Heart muscle

serum, the next large one in the lung and the very small one in the brain. The time when the concentration reaches the highest level is from about 30 minutes to 1 hour after intramuscular injection. The concentration of PC is detectable in the muscle after the administration, up to 12 hours in the pancreas and the heart muscle, and up to 24 hours in the other organs.

The distribution of dihydrostreptomycin in chickens after the oral administration of the same quantity of the antibiotic as it is applied intramuscularly is shown in Table 11 where the concentration decreases in order of the bile, the kidney, the serum, the spleen and the muscle.

The time when the concentration reaches the peak level varies from 30 miutes to 2

Table 11. Distribution of dihydrostreptomycin sulfate after oral administration (Ninomiya et al.)

Organ	Time						Cont.
	10 m	30 m	1 hr	2 hrs	6 hrs	24 hrs	
Serum	* 0.57	3.3	5.16	3.7	0.39	—	—
Muscle	—	1.9	1.95	1.85	—	—	—
Lung	—	—	1.9	1.55	1.5	—	—
Liver	—	—	—	1.5	—	—	—
Bile	9.5	40.5	6.9	4.95	4.0	2.4	—
Spleen	—	3.1	2.05	—	—	—	—
Pancreas	10	11.4	5	10.5	—	—	—
Testis	—	—	—	—	—	—	—
Kidney	—	3.4	3.4	6.0	2.7	2.0	—
Heart**	—	—	—	—	—	—	—
Brain	—	—	—	—	—	—	—
· Crop	2,700	1,331.3	1,875.0	68.3	2.3	1.4	—
· Gizzard	843.8	795.0	446.3	36.8	0.87	0.42	—
· Small intestine	1,087.0	2,362.5	1,209.4	204.4	47.3	38.3	—
· Cecum	—	1.41	54.4	1,462.5	2,062.5	572.5	—
· Rectum	—	0.68	543.8	5,400.0	352.5	130.3	—

Remarks: * mcg(pot.)/g or ml ** Heart muscle · The feed material contained in them—None or bellow certifiable concentration

Dosage: Dihydrostreptomycin sulfate 100mg(pot.)/10ml/kg body weight

Table 12. Distribution of tetracycline in chickens after intramuscular injection (Ninomiya et al.)

Organ	Time										Cont.
	5 m	10 m	20 m	30 m	1 hr	2 hrs	3 hrs	6 hrs	12 hrs	24 hrs	
Serum	89.4*	67.5	45.9	56.0	26.5	8.8	4.9	2.6	1.6	1.5	—
Muscle	2.4	2.7	3.9	8.8	10.3	8.3	11.5	9.0	5.3	5.0	—
Lung	45.0	41.0	48.0	59.0	29.5	10.0	9.0	6.0	2.9	2.6	—
Liver	46.0	44.0	55.0	77.5	82.5	29.0	17.8	10.0	4.0	3.4	—
Bile	25.3	28.0	33.3	161.7	451.7	491.7	478.8	666.7	704.2	458.8	—
Spleen	32.0	27.0	29.0	44.0	17.3	6.3	4.5	3.2	2.3	1.6	—
Pancreas	10.0	7.8	12.0	18.8	14.3	8.1	4.6	3.5	2.7	1.3	—
Testis	9.3	6.5	15.0	18.8	11.5	6.6	5.5	4.0	1.8	1.3	—
Kidney	286.3	360.0	433.8	602.5	612.5	412.5	331.3	40.0	30.9	11.1	—
Heart	36.1	33.5	31.5	35.0	27.0	9.5	8.3	3.8	2.7	2.1	—
Brain	1.8	1.6	1.3	2.0	1.1	0.7	<0.5	<0.5	—	—	—

Note: TC 100mg/kg(B.W.) * mcg(pot.)/g or ml

hours after the administration. The organs where DSM cannot be detected through the whole process are the brain, the heart muscle and the testis. The above-mentioned results are similar to those which Ninomiya, et al.[1], have reported their experimental results on a goat, and it also does not differ very much from those which Weinstein, et al.[5], have reported.

3) Tetracycline

The distribution of TC in chickens after the intramuscular injection of it with the dose of 100 mg/kg, B.W. is shown in Table 12 where the concentration decreases in order of the bile, the kidney, the serum,

the liver, the lung, the spleen, the heart muscle, the pancreas, the testis, the muscle and the brain. The time when the concentration reaches to the maximum value after the injection is 5 minutes in the serum, 6 to 12 hours in the bile and about 30 minutes in the other organs.

The distribution of TC in chickens after the oral administration of the same quantity of the antibiotic by the intramscular injection, is shown in Table 13 where the concentration is accepted in every organ except in the brain, but it is low in the serum, the spleen and the testis, etc., and it disappears in a short time.

The concentration of TC in the kidney, the bile, the lung and the liver, etc. increases after 1 to 2 hours after the administration but after that it decreases rapidly. These results agree in many points with those which Ninomiya, et al.[6], have reported their experimental results on goats, with the concentration in the blood of human being and various animals which Dowling and Musselman[8] have summarized, with those which Ullberg[2] has experimented using mice, and with the other results.

4) Summary

The above mentioned are the outline of the actual conditions of antibiotics used for animals in Japan and at the same time the problems concerning antibiotic residue which are experimentally and theoretically solved, are summarized on a basis of the experimental results.

In this report, I have introduced only the results of studies on PC, TC and DSM which are used most commonly for animals, out of many almost the same type of experiments which have been undertaken by authors, et al., since 1956, altering the experimental conditions such as the kind of antibiotics, the shape of preparation, the course of administration and the kind of animals.

As clarified from these results, the distribution of concentration of antibiotics in the living body varies remarkably with the course of administration, of which difference is especially remarkable in cases of PC and DSM. Aminoglycosidic antibiotics

Table 13. Distribution of tetracycline in chickens after oral administration (Ninomiya et al.)

Organ	Time						Cont.
	10 m	30 m	1 hr	2 hrs	6 hrs	24 hrs	
Serum	0.79	1.95	4.05	1.97	0	0	0
Muscle	0	0.48	2.1	2.34	1.68	0.41	0
Lung	0.72	4.5	6.0	20.25	0.42	0	0
Liver	0.9	7.2	15.75	9.9	0.9	0.57	0
Bile	1.5	39.0	78.0	84.0	12.45	11.4	0
Spleen	0	1.5	5.25	3.15	0	0	0
Pancreas	0	1.32	4.05	4.2	0.75	0	0
Testis	0	1.23	3.3	1.41	0	0	0
Kidney	5.1	34.5	202.5	70.5	4.8	1.29	0
Heart muscle	0	4.05	6.45	4.5	0.63	0	0
Brain	0	0	0	0	0	0	0
Crop	7,218.5	4,031.5	3,225.0	1,414.0	9.9	6.23	0
Gizzard	1,932.0	1,388.0	838.0	190.0	15.0	3.38	0
Small intestine	486.0	921.0	2,300.0	140.3	20.9	0.57	0
Cecum	1.08	1.3	4.2	7.7	664.0	475.0	0
Rectum	0.96	6.3	7.2	275.0	229.0	45.0	0

Note Dosage, 100 mg/10 ml/kg (B.W.)

such as KM, DM and HM which are the same series as DSM, peptide antibiotics such as BC, CL, MK, TP, VM and PM etc. have a common characteristic that it is hard to be absorbed by the oral administration. In case of tetracycline antibiotics which are orally used as a rule, however, their absorption and the distribution in chickens by the oral administration are extremely low compared with the result by the intramuscular injection. It is recognized that there is a close relationship between the concentration absorbed and the length of time to maintain the detectable concentration of the drug. It can be concluded that the administration way has close connection with the concentration absorbed in body. We cannot obtain the high concentration of the drug in blood when antibiotic is administered orally. That is, there is a limit in the concentration in the blood which is obtained by the oral administration.

These results are procured by using the concerned antibiotics which are dissolved in water in order to simplify the experimental conditions. Consequently, it might be different from a case of a special drug, that is, the one which is prepared for the purpose of extending the time of maintainance of antibiotics in the living body used. Most of these special drugs, however, are ones which the absorption speed into the body is restricted by the technique of compounding medicines. It could be considered that the fate of the antibiotics in the body after the stage where it is absorbed into the living body is similar in any case. It is presumed that there exists a series of common conditions in the ones which is not only antibiotics but also various drugs remain in the living body[9].

Sasaki, et al.[10], have reported that the duration of remaining of PC in the body becomes longer when the symptom is severe, concluding his experiments of pneumococcus which is inoculated to mice. There is a general tendency that a greater amount of drug diffuses and remains longer in the inflammatory tissues than in the case of normal tissue, and such phenomenon is not restricted only to antibiotics but it is observed in other drugs.

If the animal has some type of disorder in the excretory passage, etc. on account of the ill effects of the drug concerned, the concentration in the blood would abnormally increase, and the drug would be maintained in the blood and body for a long time. It is difficult to summarize the other minor conditions related to the residue, etc., since they are complicated so much.

It should be said, however, that the pattern of distribution of antibiotics in the living body is unexpectedly simple beyond expectations. Moreover, the amount of drug transition to major edible tissues, which can be used as animal food product, is generally small, and the residual time in the muscle tissue is remarkably shorter than that in the blood and others.

From the above description, we can conclude that the residue of antibiotic in the living body must remain slightly hazardous, if it is administered theoretically with the skilful knowledge about each antibiotic. But the point to which more attention should be focused in using antibiotics for animal are the development of the resistant bacteria for antibiotics and other chemotherapeutic agents and the transmission of the character. These problems are so complicated that much investigation is required to solve them completely by combining with stock-raising. There is an opinion that the problems about anaphylaxis could be solved by removing the residue of antibiotics in livestock products.

Antibiotics have greatly contributed to today's stock-raising management. It is considered that the present high productivity of stock-raising is due to the high efficacy of antibiotics applied to the animals. On the other hand, antibiotics have become an

object of major interest of the persons concerned along with the increasing consumption amount of antibiotics for animals' use.

The antibiotics, which have been considered to be low in virulence and ill effects in spite of their high efficacy, are now being sharply criticized. It is very important to solve the problems about the hazardous reaction of antibiotics applied to livestock and not as that in a specific country but as that in the world.

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