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PRESENT STATUS OF RABBIT ENTERIC DISEASE RESEARCH

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Introduction

It is an undoubted fact that the rearing losses of rabbit management are mostly caused by the enteric diseases and the several forms of pasteurellosis. With the expression of my gratitude for this comission in this introductory paper I would liketo deal only with enteric diseases for the following reasons:

1./ The etiology of several forms of pasteurellosis has been more or less elicited in the last decade / Weisbroth 1974, Rossi 1976, Spanoghe 1978, Morisse 1978 and 1979, and Hippe 1982/ and its etiology is accepted generally and widely. The resulting damage does exist nowadays too, however this problem should be solved with the preparation of an efficient vaccine working in an optimal climatical environment /Morisse 1978/. The importance of these problems will probably be more emphasized in the angora wool production in the future.

2./ In the complex group of enteric diseases there are some questions pending at present time both in the teminology and in the etiology which is shown in the

figure 1. It can be seen that beside the identical, well known symptoms a number of different terms were described. The questions have been more complicated because beside the exactly similar symptoms, different agents were isolated and reported as a new disease, according to the well-known methods and instruments of the several authors. In the figure 1. the symptoms are described with a word for word quotation from Greenham /1962/ and we have to state that even after twenty years they are still timely.

3./ After a short prosperity the capital investment has diminished in the rabbit bussiness in the last few years hindering the technological and research development. The reason is that in consequence of enteric diseases we can not ready by guarantee a safe and regular rabbit meat production. We hope that this Congress will bring us nearer to the solution because it is the high time - in our own interest too,- to help the production of the more and more marketable rabbit meat.

4./ Last but not least this condition has cause the overwhelming majority of the losses for many years and even now, as it is shown in the table 1. It can be seen from the data of daily examinations, 74 per cent of the losses from the group of growings were caused by enteritis complex between 32 and 60 days of age while later, between the days 60 and 90 both of the main sources were equalised.

Since the time of Greenham desciption there was a considerable progress in many special fields of course bringing some veri interesting and usable results. Overstepping the simple registering bacteriological examinations Löliger and co-workers /1968/ were the first authors who carried out some succesessful challange, demonstrating the possibility of a complex etiology. Furthermore it was of great importance that this work separated the diarrhoea of a 4 - 10 weeks old rabbits

from the similar pathological processes of the other age groups. None of the earlier and even not all of the later papers take into consideration this important fact and all of the enteric diseases were discussed without distinction of the age of the animals. Numerous examinations were carried out later in order to elicit the etiological role of E. coli and intestinal coccidia. Some authors have attributed a basic role to clostridia and clostridial toxins and others have supposed vibrios, rota-, adeno- and rheo viruses as etiological agents. It was proved furthermore in our examinations that some cases of so called "mucoid enteritis" are not diarrhoeas but on the contrary this illness starts with a constipation. These experiments were repeated by Targowski /19 / with the same results.

In the meantime some papers referred to the appearence of Tyzzer's disease in rabbits too.

Recently some very interesting and important results were published introducing several hypothesis synthetizing the results of microbiological and pathophysiological works about the etiology of pathological processes. With the exorbitant claim of completeness I would like to summarise and/or separate these divergent opinions in order to make a foundation for future work. For a great task as this one, it might not be enough to rely on the experience of only one specialist of course and I ask you to correct my faults and I ask to be excused for my errors.

More than anything else we are in need of the unification of the terminology. Considering the existing etiological problems let me propose the term of <u>enteritis complex</u> in accordance with Cowie-Whitney /1970/. In our earlier work we were using the name of "rabbit dysentery" too, introduced by Löliger /1968/ but I suppose we may agree with Prescott's opinion /1978/ to restrict this term to the bloody diarrhoea. <u>Enteritis complex</u> is not distributed in this paper on symptomatical basis / as meteorism, watery diarrhoea, mucinous diarrhoea etc./ because within

this disease complex -as it is easily conceviable -, these symptoms may follow one another /f.e. as the consequence of constipation logically develops here a meteorism / and at the same time different symptoms may have identical etiology.

I. The common characteristics of enteritis complex

In the pathological processes both in the individual and stock course of enteritis complex there are some basic differences depending on the age of the animals. On the basis of a ten years large scale observation there is reason to differentiate the enteric diseases according to the age groups because of the different outbreak of epidemiology and control. We do not presume to say that this distribution has an etiological background also, because there is a possibility that different agents cause identical symptoms and post mortem findings in sucklings and adult rabbits respectively.

I.1. Enteritis complex in suckling rabbits

This condition may be characterized by its periodic outbreak in certain breeding houses independently of the sesonal and climatical circumstances. In large scale rabbit farms this disease causes relatively great losses from time to time. Probably because of the large farm incidence of this condition it is rarely referred to in the literature, f. e. it is not mentioned by Fisher/1979/ and Löliger /1980/ among the causes of the suckling age losses. The outbreak occurs between 7 - 14 days of age and runs its course within a 4 - 5 days period having a 100 per cent morbidity and about 50 per cent mortality of the infected litter. In a breeding house having 520 does about 20 - 30 per cent of the litters fall sick in an epidemic period.

The first symptom is the thin yellow watery diarrhoea followed by a subsequent constipation. The disease is named as a "sucklings' yellow diarrhoea" by the Hungarian

experts. The necroscopical lesions are characterized by the clotted milk filled stomach, a mild catarrhal oedema in the small intestine and veining injection of the mesentery and gut serosa. The caecum is filled with yellow fluid and gas. Non hemolitic E. coli may be isolated from most of the cases but preventive and curative antibiotical treatments -carried out on the basis of a detailed antibiogram-, proved to be ineffective.

I.2. Enteritis complex in growing rabbits

This is the well known condition which causes the greatest losses and was comprehensively discussed by several authors. In spite of this fact the matter may not be considered a sttled question. The "growing rabbit" expression in the subtitle was chosen intentionally because the connection is only apparent between the outbreak of this disease and the weaning as it is shown in the figure 2. The increasing of curves occurs in different times after weaning and in the case of a 40 days weaning, numerous losses can be registered before the weaning, too. This way we do not suppose that rabbits are "more akin to post weaning diarrhoeas" as it was reported by Prescott /1978/.

Recently a lot of detailed work was published by several authors describing the disease: - the clinical symptoms, - the post mortem findings, - the histopathological features,-the predisposing factors, - the rate of morbidity and mortality, - the non infectious nature of it, in classical sense of this term.

It does not seem necessary to repeat the authors in this place even although smaller or larger differences do exist among the descriptions. These are planned to be discussed in the following chapters of this paper.

I.3. Enteritis complex in adult rabbits

Two forms of enteritis complex occur in adult animals:

a./ an acute diarrhoea corresponding to the condition mentioned above in growings, but the outbreak can be

found sporadically both in the large scale stocks and backyard systems.

b./ an enteric disorder characterized by heavy mucinous intestinal secretion connected with a constipation. It is often named in the literature as "mucoid enteritis" or "mucoid enteropaty".

This disease was frequently confusedwith the diarrhoea of growing rabbits because of the occasionally mucinous appearance of this latter. In our former large scale farm experience we have met this condition in some cases when its cuorse looked to be epidemical with the following characteristics:

a./ The outbreak appeared following the first or secund parturition of does within a year from the introduction of a new rabbit farms.

b./ The condition spread after a few weeks from stall to stall and about 70 per cent of the breeding houses became "infected".

c./ The illness of does started about 3 - 7 days after parturition

d./ A mucine accumulation and dry greenish-black contents were seen in the large intestine as a post mortem lesion but this latter was not always detectable signifying that the mucine accumulation may happen during a half day period also. In such a short time the drying up of the content of caeca may not come forth of course. A fatty infiltration of the liver was sometime seen.

e./ The death was preceded by a 4 - 6 days constipation of which the symptom is a lack of dejection. In the absence of other observable symptoms the morning veterinary visit can locate the ill animals by the lack of dejection 4 - 6 days before death.

f./ E. coli may have been isolated in most of the cases but the antibiotic treatment and prevention proved to be ineffectiv.

g./The feed supplementation with carrot and ad libitum roughage looked to give good results in the prevention if

it was applied during pregnancy. There is a possibility of course that this control appeared effective only because the "epidemic" by than has run its course anyhow.

h./ The disease had never spread from does to their sucklings. These remained healthy in nursing following the death of does.

i./ The constipation is usually followed by the death of does while recovery occurs in a few per cent only. In such cases after a 4 - 10 days constipation the dejection starts with small black drops of faeces returning to normality after a few days.

j./ During the period of constipation the accumulated mucine drops from the rectum in a passive way by the moving of the sick animal having appearence of mucinous diarrhoea. There were many authors earlier deceived by this phenomenon.

k./ The mucin accumulation was obtained experimentally following ligation of the proximal colon /Sinkovics 1976, Toofanian 1983./.

Beside this age group distribution we should like to discuss the role of some of the incriminated agents in details. Because of the extant losses in most rabbitries I am obliged to believe that in spite of our somewhat suggestive work we still have not got the proper solution. I do not want to discuss anybody's results and theories but I feel it my duty to endeavour for the sake of our common business to search the counter arguments against all supposedy pathogenic agents in the forthcoming parts of this paper. I suppose we have to agree with Prescott's /1978/ opinion mentioning in his general paper the reports of rabbit intestinal disprders which "are suggestive rather than conclusive".

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II. The role of E. coli in enteritis complex

E. coli is reported mostly in the literature as a causative agent when it is concerned about any one of age groups. Its origin is first of all the undoubted fact that E.coli may be isolated easiest from the content of the sick animals intestine. This germ can only be demonstrated in the case of healthy rabbits by enrichment methods and is is rarely found by conventional dilutant technique or direct culturing methods / Smith 1965/.

In the first general reports /Greenham 1962, Ostler 1961/ the role of this germ was considered secondary only but the subsequent works / Matthes 1969, Glantz 1970, Vetési 1970, Weber 1971, Kosenok 1974, Rossi 1974, Shmidov 1975, Matthes 1976, Gallazzi 1980/ presumed that it is an exclusive and most important causative agent. There are some objections however which made these assumptions questionable.

II.1. The lack of enterotoxin production

There is no doubt today that most of the isolated strains do not produce heat labile or heat stabile enterotoxin none of the bacteria have K 88 or K 99 antigen and they do not agglutinate the rabbit red blood cells /Varga 1982 /. At the same time the releasing of endotoxin is not especially characteristic of E. coli, furthermore it may be isolated in different quantity from the cases of animals died in enteritis complex. It means also the different quantity of endotoxin at the given moment. These non-haemolytic germs may be present however in a relatively great number in the intestinal flora of healthy animals too, without any clinical symptom / Christ-Vietor 1973/. Beside this certain authors implicated several types of O antigens / O 33, O 77, O 85, O 101, O 103, O 119, O 128, O 132 etc./ and a few of them / O 1, O 2, and O 86/ were described as a cause of suckling rabbit saepticaemia /Kulshrestha 1977/.

In spite of many descriptions the E. coli can never be found in "pure culture" in the intestinal content because other bacteria f.e. the members of bacteroides group -, overgrow it always /Sinkovics 1978/b./. Furthermore depending on the method of isolation other endotoxin consisting germs may also be cultivated from the gut flora which may have an important role in pathogenic processes /Vörös 1980/.
We have to have some doubts about those results too, which account for the lack of oocysts simultaneously with the E. coli infection. With reference to the works of several authors /see later/ we are convinced that the coccidial oocysts may always be numbered though in different quantities in the faeces of growing rabbits using a McMaster or Schütze counting chamber.

II.2. The questions of the prevention and treatment

The prevention and treatment have never been perfect on the basis of the E. coli theory though this should have been the elementary evidence as regards the pathological role of this germ. Only a few authors could account for successful treatments or prevention /Cowie-Whitney 1974, Rossi 1974, Morisse 1978/ but these descriptions are kacking either in model experiments or field trials or stting a control group. As there is a 50 per cent inclination of this disease to recovery /figure 2.- 5./ setting up a control group would have been desirable. Noting that even the mentioned authors were probably not satisfied working on the basis of E. coli conception, and because of that they were looking for other methods. Morisse /1978/ f.e. had reported good results by using of Colistin + Buscopan therapy, but he got better results in his latter work administering acetic acid and lactulose /1980/.
Italian authors / Facchin 1980/ and Prohaszka / 1980 / who were earlier convinced about the primary role of E. coli, in their newest report are looking for the

solution in the correct hydromineral balance or the elimination of consecutive alcalosis. One has to point out however that these recommendations can not considered to be specific as regards to E. coli.

Finally let me allow to refer to a series of our own works in which we reported the uselessness or both the preventive and curative treatments carried out on the basis of precise antibiograms, using large experimental groups, performing model experiments, trying a series of antibiotics. Taking the opportunity of some large scale rabbit farms we set up such a number of control animals as seemed to be necessary for this examinations, and had medicated pellets according to the claims a possible good prevention /Sinkovics 1978 a, b and c/. We started this work believing in a bacterial background of enteritis complex, especially in the E. coli, and finished it with a complete failure.

If the E. coli theory would be well established we should have got some small result as it might have been expected on the basis the thirthy years experience of human and veterinary practice.

II.3.The questions of challange experiments

Most of the authors satisfied with the results of isolation completing it with the determination of serological groups,did not perform challange experiments or because of their faliure these remained unpublished. There is a small number of reports in the literature showing a failure of challange infections /Prohászka 1972/ though these were certainly carried out by many specialists.

All of the reported successful challanges claimed some accessory circumstances in order to achieve some results, but at the same time these disturbing elements make it difficult to accept them without reservation.

In some parts of challanges the rate of the successful infections is very low. Varga /1982/ related an experimental oral infection in which only 46.6 per cent losses could have been demonstrated after a few days combined administration of E. coli and NaOH.

Vetési /1974/ could also register some losses, but his experimental animals were fed with a pellet consisting of 6 /!/ per cent crude fibre. The death of rabbits after 28, 39 and 41 days of the cahallange was considered positively by him, but such long time is not acceptable in the case of bacterial infection in such feeding circumstances.

In some other publications there are mentioned certain external factors which have been parrallel with the E. coli administration as the cooling to -20°C /!/ Yuill 1965/ coccidial infection / Löliger 1968, Hoffman 1973/ prednisolon injection / van Kruiningen 1972/ and the above mentioned NaOH or low fibre content of the pellet. It is worth mentioning that the results of combined infections with intestinal coccidia may certainly be only accidental, because the pathogenic strains of coccidia were unknown at that time. Using of E. media magna and E. media + E. coli Varga /1982/ was not able to repeat these results.

Morisse /1978/ elicited a "colibacillosis type enteritis" with the overdosage of ampicillin but we do not envisage the connection of such different matters conclusive.

Prescott's /1978/ examination with the intestinal inoculation of E. coli O 153 proved without any doubt only that the release of endotoxin may occur from this germ also. The future examinations employing this excellent experimental method will perhaps answer our present questions. The intestinal inoculations of several agents /other bacteria, fungi and viruses/ may help us chose the most important ones among these.

The experiments in which swine or human pathogenic enterotoxin producing strains were administered orally or inoculated in the intestine are not acceptable. The pathogenity of these swine or human origin strains was here repetedly proved, and the role of the rabbits in these examinations has no more importance than a laboratory model animal / Sherr 1973, Metz 1974, Vetési 1974/. The problem is that these authors spesk in their conclusions about

"successful" experimental infections of rabbit and others adopted this opinion as an evidence.
We rather suppose that the insufficiency of the examinations working with E. coli strains led them to resort to such strains which have never been isolated from sick or dead rabbits.
In spite of all scruples and objections it is possible of course that E. coli will prove the most incriminated agent after all but we are in need of stronger evidences in future and better results in the field control.

III. The role of Bacillus piliformis in the enteritis complex

The disease was first described by Tyzzer /1917/ in Japanese waltzing mice. It was been later reported in other species incuding gerbils, rats, hamsters, muskrats, rhesus monkeys, cats, dogs and horses. Van Kruiningen /1971/ speculated on the possibility that it might also affect man. Now we are interested in the works in which the " Tyzzer's disease syndroma" is described in rabbits as an independent disease in itself or as a main component of enteritis complex.
I must begun with the fact that the clinical findings of Tyzzer's disease in rabbits are closely similar to the ones that were reported by Greenham /1962/ and others /figure 1./. The literature is not so abundant as it has been in the case of E.coli but the papers published in the last decade worked with well developed methods. Through these more apparent evidences were advocated but in spite of these suggestions there is some scepticism with the authors themselves.

III.1. The problems of differential diagnosis

Most of the authors did not endeavour to isolate simultaneously other agents which have earlier considered pathogenic beside this intracytoplasmatically growing

bacterium /B.piliformis/. Schoenbaum /1976/ had mentioned a moderate infestation of coccidia parallel with an efficient sulphonamide treatment but this fact is held without conclusions in this report. It is very interested furthermore, that even some of the experienced authors /Vetési, 1978, Prescott 1979/ - reporting the occurence of Tyzzer's disease in rabbits -, only refer to the presence of a great number of E. coli /10^8/g of chime/ in the intestine though in their earlier works they were convinced about the primary pathogenic role of this bacterium. Beside this Vetési /1978/ recounts the possible absence of coccidiostatic treatment among predisposing factors so that is having a disease which may be controlled by the elimination of other agent.

Italian authors /Facchin et al. 1978/ wrote about the occurence of Tyzzer's disease in North Italy too, but at the same time they did not mention at all the probable presence of E. coli which germ had been implicated earlier. The control recommended by them scarcely differs from that which was proved to be effective in the cases of " E. coli bacillosis". The situation is perfectly characterized by Thunert /1978/ stating in his paper about Tyzzer's disease that this condition was mostly described as a coli enteritis. We should expect a differential diagnosis on the basis of which range examinations from the above mentioned authors in the future since they have much experience working with both diseases.

III.2. Prevention and control

The attempts to prevent or control this disease are in need of the laboratory examinations or field trials or control groups or in most of the cases only the field trials are described. Vetési /1978/ thought the coccidiostatic treatment to be important in the control, but Shoenbaum /1976/ guessed the sulphonamides had a predisposing function for outbreak. He found the oxytetracycline highly effective, Simon /1977/ however expressed

the view that the chloramphenicol and oxytetracycline did not reduce mortality. Similar faliure was described in the treatment by Niven /1968/ but on the contrary van Kruiningen /1971/ reported the end of the epidemic after 36 hours following an initial administration of oxytetracycline.

III.3. The problems of experimental reproduction

There are similar contradictions in the reproduction of this disease when the authors endeavoured such trials anyhow.

Summarizing the data we have to say that the challanges are successful but only in mice and rats /Schroich-Fries 1978 and 1979/ but some experimental manipulations / Prednisolon treatment, Xradiation or fluctuation of temperature/ were necessary for a successful challange. Regarding the experimental infections Thunert's /1978/ statment seems to be important according to which the mice might not be infected successfully by the liver homogenisate of rabbit. The question is raised wether it is not an actual laboratory mice disease declared to be a non-existant rabbit illness because of the apparent similarity.

Against this view we should consider Schroich-Fries's /1978 and 1979/ works who tested rabbits sera with a mice derived antigen and in some rabbits had high antibody titres. It is true that these animals later died with no signs of Tyzzer's disease and there were not found any specific lesions at the post mortem examinations. Ganaway /1976/ also reported a serum positivity in cottontail rabbits and carried out a successful challange with 10 ELD_{50} of B. piliformis spores, but earlier/1971/ he could not account for the same results in domestic rabbits.

Facchin /1978/ isolated and cultivated these bacteria in the yolk sac of embrionated hen's eggs but the challenge failed.

We have to mention at last that the taxonomic position

of this bacterium remained unresolved. Some authors write about the germ as anaerobic sporeforming rods while Simon /1977/ attempted a successful aerobic isolation of human blood media of a vacuolated /!/ Gram labile filaments from the cases of Tyzzer's disease. He does not mention the spore formation although he published a detailed work including carbohydrate reactions morphology and staining characteristic of this organism. Now I should like to have you remember the normal intestinal flora of rabbits containing a large number of the bacteroides groups. Some of them seem closely similar to B. piliformis in their morphology /f. e. Fusobacteria/ - furthermore they have strict anaerobic characteristics, preferring to grow deep in the tissues.
The very scepticism of the authors is expressed by Schroich-Fries /1979/ writing about the B. piliformis caused gross and microscopical lesions: "these changes may also caused by other agents and the problem deserves further investigations."

IV. The role of other agents in the enteritis complex

IV.1. Clostridia

A spontaneous enterotoxaemia caused by several types of Clostridium perfringens have been described in guinea pigs, mice, hamsters, chinchillas, broyler chickens, pigs and mostly in sheep with a diet rich in carbohydrates. The occurence of clostridia in rabbits with enteritis complex was alredy reported by Ostler /1961/ but it had been mentioned earlier also / Morcos 1932, Bosworth 1943/. The clostridia appeared to be forgotten later, it must have been rarely demonstrated in virtue of its anaerobic character.
In the course of our detailed bacteriological examinations of 210 growings which died in enteritis complex both the spores and vegetative cells of clostridia showed

a great multiplication in the ileum and caecum /Sinkovics 1978 /. This fact was unfortunately minimized by us because there were only 5 per cent of all cases in which the exclusive multiplication of clostridia was observable after a few hours of death.

Excellent papers were recently published detecting clostridial toxins in the caecum and these results were affirmed by toxicity and toxin neutralization tests /Patton 1978, Rehg 1981 and 1982, La Mount 1979 and Yalcin 1976/.

The similarity of symptoms described in our former chapters has been recognizable again. Kunstyr /1975/ had reported a spontaneous infection by Cl. perfringens type A and the article waslater supplemented by the author : " on the base of additional hystological examinations could Tyzzer's disease be excluded". This addition was manifested owing to the subsequemt hystological examination also but the overwhelming majority of the works aimed only : the recovery of clostridia or clostridial toxins.

Yalcin /1976/ announced that the isolation of clostridia was frequently associated with a "coli mucoid enteritis" but in other works there was no effort to find other agents.

Patton /1980/ mentioned in his work that with special stains he could not reveal the presence of intracellular bacteria and beside undoubtable recording of iota toxin in the caeca, E. coli had frequently been isolated in a great number from the intestinal content. The challenge experiment in his study remained ineffective.

Cowie-Whitney /1970/ gives account of vaccination programm utilizing Cl. perfringens types A B and D but this specufic prevention failed to influence the mortality. At the same time it was reported to be successful by Moore /1975/ in a chinchilla farm.

The positivity of toxicity tests can not be too highly estimated because the strong biological toxins must kill naturally the laboratory animals. There is a great difference however, as this toxin is produced on a synthetic medium

or in the lumen of a spontaneous infected animals intestine.

Referring to the "antibiotic induced coli bacillosis" there are some authors also who describe a Cl. perfringens or Cl. difficile enterotoxaemia subsequent to antibiotic treatment /Bartlett 1978, Rehg 1981/.

Cl. perfringens iota toxin and Cl. difficile toxin are considered as a causative factor by Rehg /1982/ also but he wrote about a "lincomycin associated colitis" and this term seems to be in accordance with Schateman /1977/ who reported that the bacterial analysis after antibiotic overdosage gave variable and inconclusive results because of a disturbance of bacterial equilirium. We can thus examine the pathological processes of diarrhoea of course but this examination could not have any reference to bacteria.

Ending the survey of pathogenic role of clostridia we have to point out the presence of several clostridial toxins in the caecal content of diseased animals means a strong proof for the pathological rôle of them. We hope that an effective clostridial vaccine /or antitoxin of course/ will be able to convince us in the laboratory examination and field trials respectively about the rightness of this theory.

IV.2. Other bacteria and fungi

Other bacteria, as salmonellas, vibrios and Haemophylus paracuniculus /Targowsky 1979/ were sometimes supposed to be involved as causative agents of enteritis complex. We have to say however that some of these works left a few questions open some of which may become a basis for a theory in the future.

After initial Tyzzer's disease outbreak Moon /1974/ observed a similar condition another summer but B. piliformis was not recognizable. E. coli was counted in 10^3/g quantity in the jejunal content but it was considered negligable by the authors. Vibrios were incriminated as possible causative agents which were demonstrable by Levaditi stain and electron micrograph on the surface

epithelium and in the crypts lumen. While the isolation and challange experiments were not evem attempted for reproduction but this work may be a new direction in the etiology but neither Moon and co-workers nor other authors tried to confirm these results since that time. Thay did not find coccidial oocysts in the gut content but we have to be in doubt about it as I mentioned elsewhere.

The authors who have supposed a pathogenic role of salmonellas did not investigate the presence of other bacteria or coccidia either.

Gusev /1961/ reported the infection of large scale flocks by S. typhy murium but he admits the uselessness of antibiotics in the control of disease. Szemerédi/1965/ observed in a salmonella infection in rabbits followed by hyper-anemic livers with yellowish necrotic foci and pneumonia. The description indicates the possibility of parallel isolation of B. piliformis and pasteurellas if the author would have endavoured such isolation. Sadek's /1970/ report in the post mortem findings also regards such lesions which could have been described as a Tyzzer's disease by the authors who belived in the existence of this disease. All of these would not have meant any problem but the descriptions were adopted in the literature as facts as original diseases of rabbits.

The investigation of the causative role of yeasts and moulds may bring us many interesting results in the future. Saccharomycopsis guttulata is recognizable without any doubt in great number in the caeca of growing rabbits, especially in the case of <u>enteritis complex</u>. Some authors with reference of Burgisser /1961/ and Richle /1961/ speak about "saccharomycosis" as a separate form of rabbit diarrhoeas. The fact was completely omitted that the mentioned authors in their detailed examinations did not provoke either symptoms or losses by the oral or iv. /!/ administration of pure cultures of these yeasts. Burgisser's /1961/ conclusion similarly was not overtaken, that the increased numbers of yeasts

in the rabbit with enteritis complex appeared to be a sequel to rather a cause of the disease. Herman /1964/ describing a "mucormycosis" found necrotic ulcerative lesions in the mucosa of ileum and colon and in the liver. These findings were supported by histological examinations when hyphae where demonstrable in stained intestinal sections. The followers of the theory of an independent entity of Tyzzer's disease must have some questions about this mucormycosis and vica versa.
Othervise even if we have no doubt about Herman's data we have to convey the suggestion that in the cases of such intestinal mucosal lesions different specific or common germs can get trough to the mesenteric nodes and liver, inducing the development larger or smaller necrotic foci in this organs. But it does not follow from this that these agents would have been the causes of any kind of various pathologic forms /gut lesions, diarrhoea, necrosis etc./.

There are two things however in connection with the yeasts and moulds fungi which have to command interest nowadays and in the future as well. One of them is the rabbit food infection by fungi increased in the agricultural products or as a result of inappropriate storage, - the other is an uncontrolled and mass antibiotic supplementation which means a greater danger for rabbits than for other animals. These two factors may be combined in medicated and industrially produced rabbit pellets.

This problem was lately recognised in its complexity by a research team in Celle /Dahle 1981, Schröder 1982/. Furthermore one should consider as well, that following the intestinal increase of fungi and yeasts also may play a role in the pathological processes following the antibiotic treatment beside the E. coli and clostridia.

IV.3. Viruses

Recently several viruses were recovered successfully by direct and indirect methods in certain cases of enteritis complex. Adeno-, / Bodon 1980/, rota-, /Kudron

1982, Morisse 1982/ reo-, /Vetési 1982/ corona-, / Osterhaus 1982/ and other viruses were recognized in healthy and diseased animals. Some of the authors who were earlier convinced of the primary role of E. coli now have taken a contrary opinion, or did not even any attempt the isolation of this earlier emphasized germ.
Morisse /1982/ in his excellent paper about rota viruses carried out successful examinations in both direction of E. coli and intestinal coccidia and even accounted a failure of challenge. In his hypothesis the intestinal proliferation of E. coli was the results of parasitizm and/or unsuitable management and feeding conditions in which the rota viruses have a synergetic action.
In another words it may mean the primary role of intestinal coccidia and it should not be left out in the practical prevention /Sinkovics 1978/.
If the primacy of the virus theory could be proved it could bring a great promise for the future by the possible production of an effective vaccine.

V. The role of intestinal coccidia in the enteritis complex

V.1 Pathology and diagnostical problems

The possible role of intestinal coccidia in the pathology of enteritis complex was well known for ages but their pathological estimate was different in the veterinary practice. The origin of this difference can be traced to the lack of two basic elements: the coccidia free rabbits and the lack of pure species of coccidia. The problem was more complicated because of the change in the rearing management of rabbits /from deep litter to wire mesh floor/ which caused the manifestation of an atypical form of rabbit intestinal coccidiosis with the disapparence of small yellowish foci in the intestinal wall. Because of the above mentioned problems the early works about the rabbit

intestinal coccidiosis gave some excellent descriptions of the morphology and the life-cycle of endogenous development /Pellérdy 1974/, but the pathological conclusions and estimate of the pathogenity have changed lately.
The disapperance of the small foci consisting mainly oocysts which were hwld earlier as decisive findings among the post mortem lesions aggregated by the omission of MacMaster egg counting technique had led to some unfortunate conclusions.
Because of this a very frequent mistake was the declaration of the full absence of coccidial oocysts in the intestinal content of growning rabbits. It is well known today from the detailed examinations of Coudert /1976/, Gallazzi 1977 and Peeters /1979/ that rather more than less oocysts can be found in the faeces or in the intestinal content of rabbits aged 3 - 12 weeks.
Starting from anthropomorphic sanitary views it was held by many specialists that the wire mesh floor alone, or even with a repeated cleaning and desinfection give a full prevention of coccidiosis. It was proved however by Ryley /1976/ working with SPF rabbits that the intake of only one oocyst could yield the 26 millions output because of the endogenous multiplication. This fact has to change our mentality taking into consideration the microbiological aspects. There is namely a great possibility for the survival and sporulation of oocysts on the small corners of wire mesh itself and among the fur of the animals. Beside this the oocysts are highly resistant to commonly used unwarranted opinion that apparently high level sanitary circumstances exclude the possibility of coccidial infections.
The misunderstandings were increased by the exclusive use of sulphonamides which has resulted a resisitance against the drugs following a failure of prevention and treatment / Gallazzi 1976, McLoughin 1974/.
Löliger's/1968/experiments about the combined infections

raise the question again about the pathologic role of intestinal coccidia in the industrialized rabbit raising and this possibility was similarly shown by out examinations also /Sinkovics 1978/.
The doubts were minimized by Coudert /1976/ when using coccidia free rabbit flocks - established by Schellenberg /1979/ - , he could produce separate infections of the different species of Eimeria. The lifecycle, the pathologic role and morphology of 8 species of rabbit intestinal coccidia were described in these works /Coudert 1976 and 1978, Licois 1976 and 1980/. Beside this Coudert and co--workers could produce challenges in such quantity as was necessary for the experiments, as the oral administration of a small number E. flavescens or E. intestinalis caused a 90 per cent mortality.

I should like to call your attention therefore to this agent as being the only one producing diarrhoea and losses among the so far dicussesd ones without having some additional manipulation.

These challenges with special regards to the post mortem gross lesions were completed by histological examinations in comparison with spontaneous cases; their detailed descriptions should contribute to the understanding of pathological processes of enteritis complex.
We are also in need of challenge using not SPF but conventional rabbits.
Coudert and the authors working similar methods / Peeters 1979, 1980 and 1981, Okerman 1980, Kutzer 1981/ carried on some successful prevention and determined the effectiveness of some coccidiostatics. Earlier the efficacy of these was not correctly measured lacking the SPF tecnics. In the meantime many new coccidiostatics /Lerbek, Cycostat, Salinomycin, Monensine, Clopidol etc./ were developed and their usage decreased the morbidity and mortality in field trials also with the complete agreement of several authors /Sambeth 1980, Licolais 1980, Varga 1980 and Peeters 1979/.
In spite of the mentioned results the correct diagnoses of

of the intestinal coccidiosis has remained problematic for the following reasons:

a./ In most of the diagnostic laboratories the Mac--Master -, or other precise egg counting technique has not become general. Because of this the laboratory reports to the practice veterinerians carried out on the basis of some guess work have frequently had misinformations abuot the rabbit real coccidial infection.

b./ The quantity of counted oocysts did unfortunately not give us essential evidence because the oral administration of 5 - 10 000 oocysts of E. intestinalis and E. flavescens means a hevy infection, while 500 000 oocysts administered of apathogenic species /E. perforans or E. neoleporis / do not cause either clinical symptoms or decreasing of body weight /Coudert 1976 and 1979/. The specification of Eimeria species cuold bring us to a decision but the diagnostic institutes and laboratories are in need of specialists of this field.

c./ The exact determination of oocysts' count in the individual cases usually means a belated diagnosis, because -as it well known -, the damaging effect to the epithelial cells is caused by schizonts and merozoits. It unfortunatelly allows the recovery of a very small number of oocysts from the faeces, while the damage is caused occasionally by millions of endogenous developing forms of coccidia.

d./ It might follow from the point c that the histological findings could help us on correct diagnosis but these findings are generally exhausted. The possible causes for this are an uncomplete knowledge of exact intestinal localisation of several species and it is impossible to make as many sections as would be necessary to investigate the whole intestinal tract.

Proceedings 3rd World Rabbit Congress, 4-8 April 1984, Rome – Italy, Vol. 2, 185-220

V.2. A hypothesis about the etiology and pathology of enteritis complex

We alredy have numerous theories about the emergence of enteritis complex and some of them have tried to give an explanation on coccidial basis. According to these theories the effect of schizonts and/or merozoits damaging the epithelial cells would be the first step in the pathological processes resulting such lesions in the intestinal wall which allow the resorption of endotoxins, exotoxins or other endogenous amines. The most recurrent problem in this theory is the very frequent failure of histological examinations regarding the mucosal lesions. However, in spite of this failure most of the rabbit specialists speaking about E. coli or B. piliformis infections could attribute an initial role of coccidia within the intestinal processes. According to our present hypothesis the development of enteritis complex has three important basic elements:

1./ Coccidial infection by pathogenic species
2./ The strong inhibition of small intestine motility
3./ The proliferation of the agents which are present in the intestinal lumen at the very moment / e.g. E. coli, clostridia, viruses etc./.

The effect of coccidia in the inhibition of intestinal motility was proved in chikens many times. Fioramonti et al. /1981/ in their very precise work reported this effect in the case of rabbit also when following an experimental E. media infection they could measure the strong inhibition of intestinal motility. So, the small intestine /and large intestine,too/ being inhibited in its motility undergoes a change into a fine culture medium incubated at 38 - 39°C, in which the proliferation of a malignant bacterial flora could start, which can be fuond in the intestine of healthy animals but only in a very small number. It is followed by the loosening of surface epithelium by the consequent

resorptions of biological toxins. The proliferation of E. coli simultaneously with the coccidial infection was stated earlier by Mosrisse also /1982/.
The described similar and various histological lesions /oedema of the submucosa, dilatation of the crypts lumen, severe necrosis etc./ become heavy or change according to the types of released toxins.
In the meantime there exist many possibilities naturally, for whatever invasisve agents to be admitted to the portal blood circulation coming to the liver and producing there necrotic foci.
The toxin and biological amine accumulation causes a periodic - sometimes heavy - diarrhoea according to the rules of pathophysiology. It would be the explanation for the very rapid outbreak of diarrhoeas / and losses/ and the variability of the results of antibiotical treatments involving the more useful coccidiostatic prevention.

The course of disease depends on the number of pathogenic coccidia, the violence of produced toxin and on the environmental factors which can influence the physiological motility of intestine.

The described processes /alcalosis, upset of mineral-, water-, electrolyte-, and acid balance, associated with the changing of carbohydrate metabolism/ are consequences of these processes.

There remains a problem that we are not able to explain all of the cases of enteritis complex on the basis of the above mentioned hypothesis. Provoking diarrhoea and losses e.g. by a very early /14 - 16 day/ weaning we could not recognise any macro- or microscopical findings, regarding the coccidial infections.
Another problem is the claim to confirm this theory by some complex experiment because we have to call the words of professor Marek to our memory:

" Real science must prove all its tenets and for that reason we shall not be allowed to declare anything for truth which would not follow spontaneously from evident and undeniable experiences and trials ...."

Proceedings 3rd World Rabbit Congress, 4-8 April 1984, Rome – Italy, Vol. 2, 185-220

Table 1. The course of enteritis complex /E.C./ in an untreated growing rabbit flock weaned on the 32. day after birth.

Weaned rabbits	no.	1296
Losses between 32. and 50. day of life	no.	222
" " " "	%	17.1
Losses from E.C. from the total	%	74.8
Losses from pasteurellosis from the total	%	25.2
Group size on the 50. day	no.	1029
Losses between 50. and 60. day of life	no.	117
" " " "	%	11.4
Losses from E.C. from the total	%	74.9
Losses from pasteurellosis from the total	%	25.1
Group size on the 60. day	no.	957
Losses between 60. and 96. day of life	no.	132
" " " "	%	13.8
Losses from E. C. from the total	%	53.3
Losses from pasteurellosis from the total	%	46.4
Group size on the 96. day	no.	855
Losses between 32. and 96. day of life	no.	471
Losses between 32. and 96. day of life	%	36.3

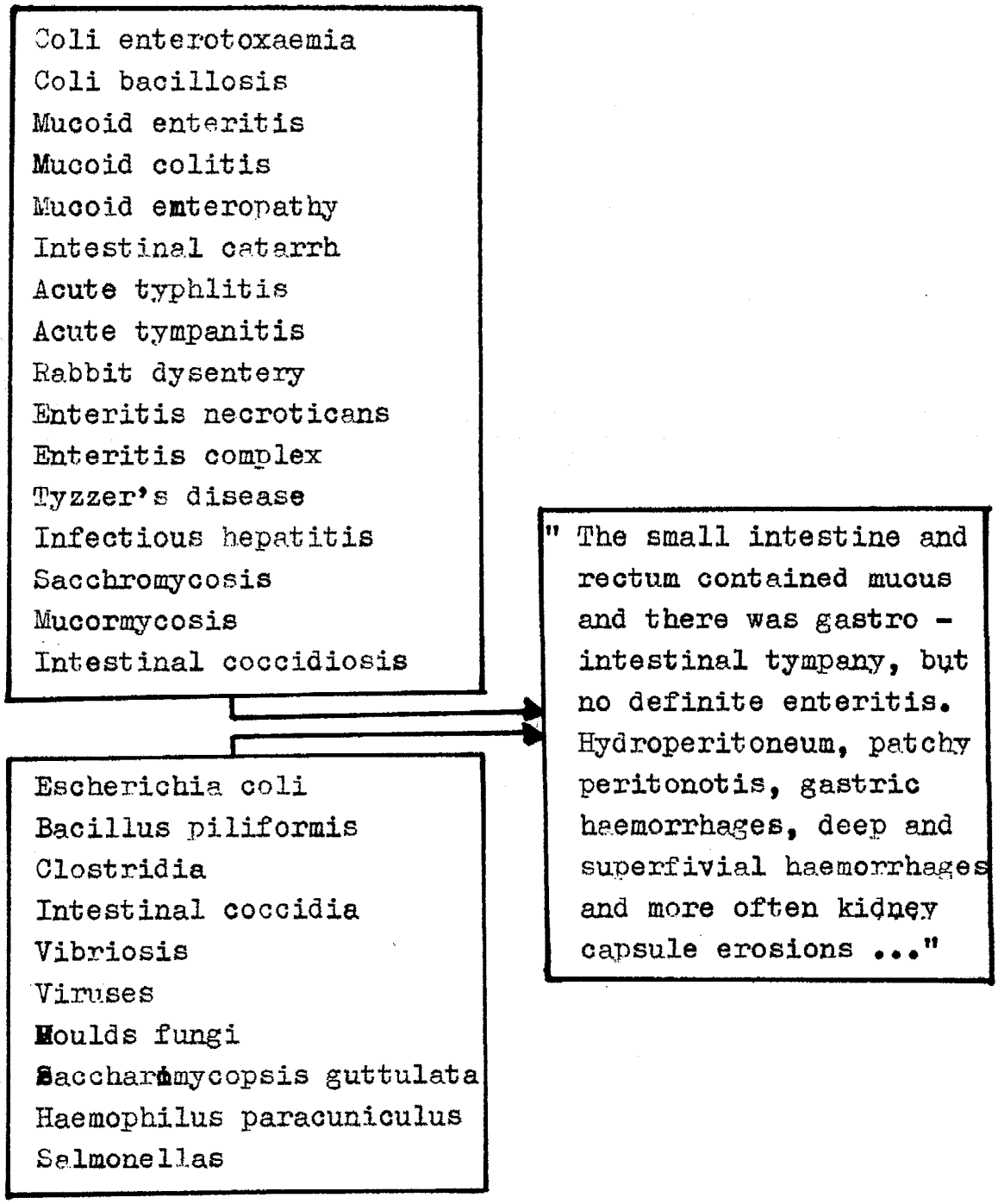


Figure 1. Different causative agents, different terms and nearly identical post mortem findings.

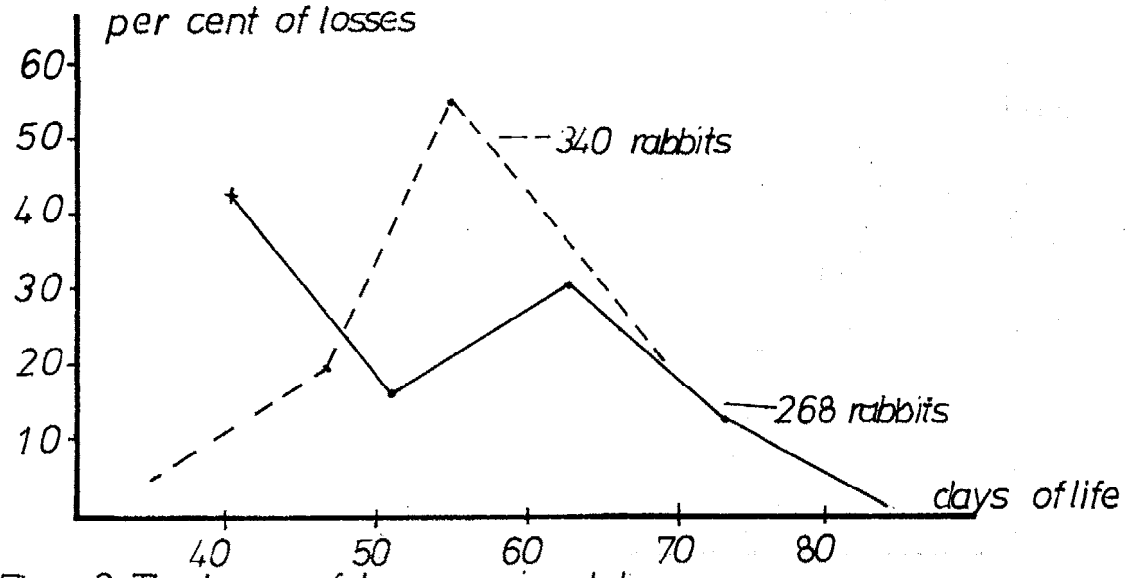
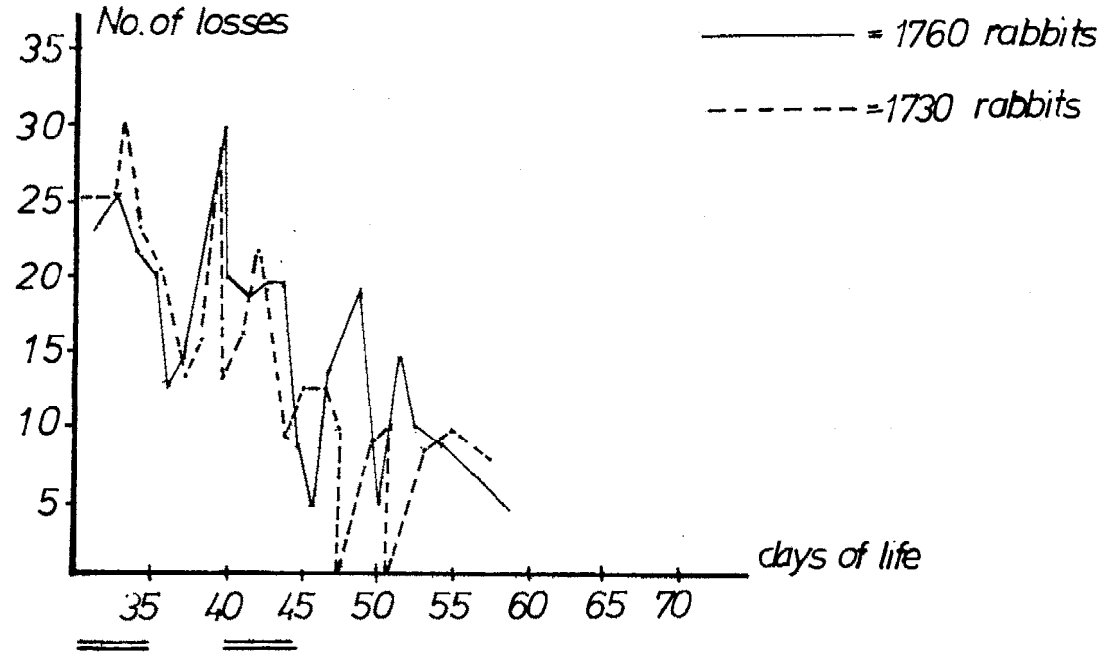


Figure 2. The losses of two experimental groups. --- summer period, —— winter period

Figure 3. The curves of morbidity /—/ and mortality /---/ in a group of 700 growing robbits.



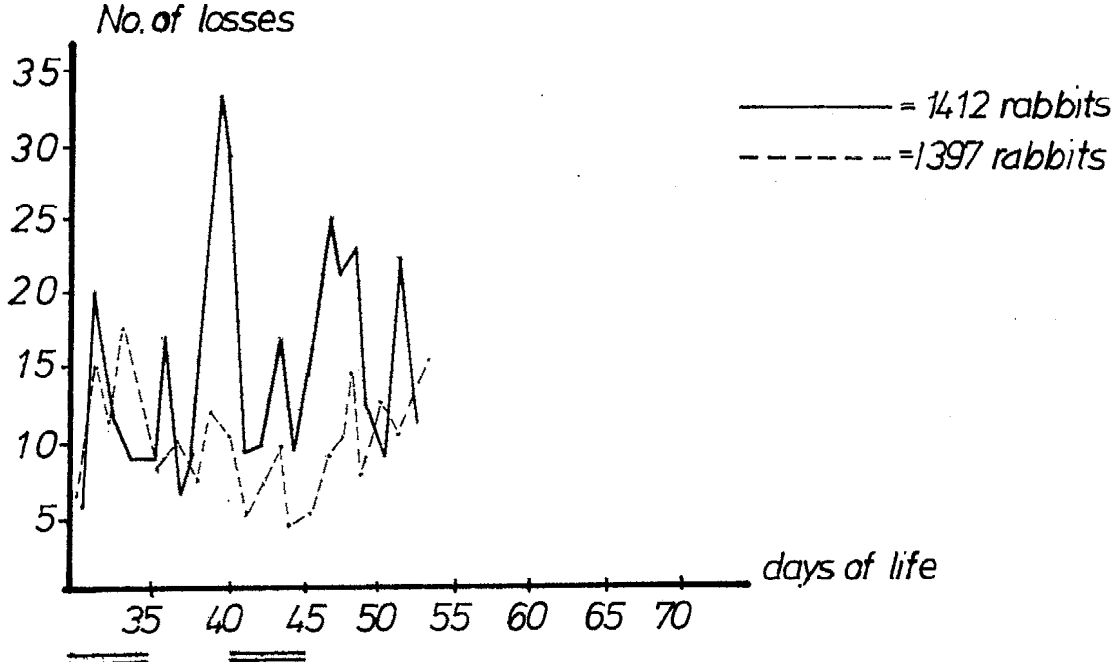


Figure 4. The effect of the sulphaguinoxalin treatment in the experimental /—/ and control /- - -/ groups.
═══ days of treatment

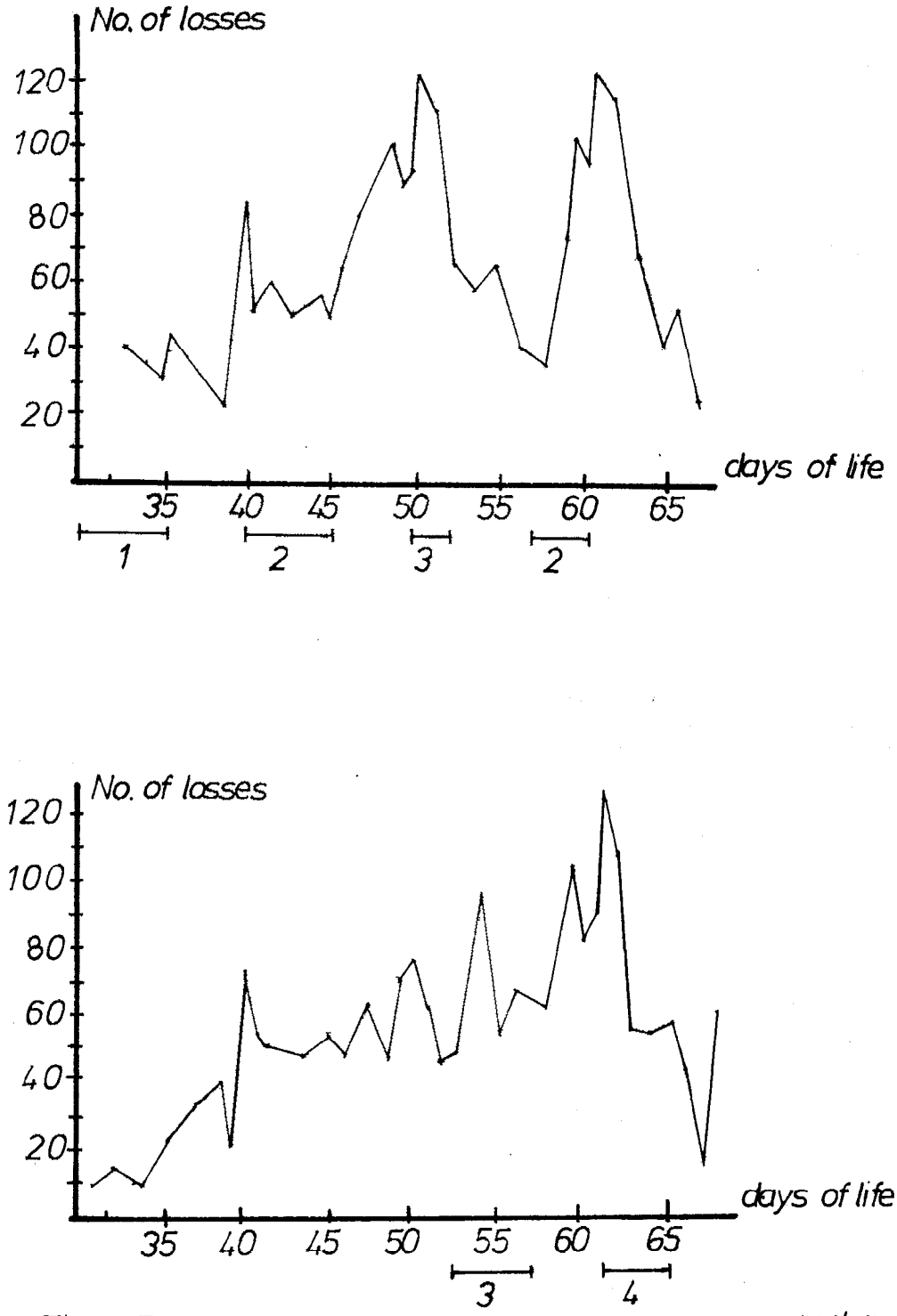


Figure 5. The curves of mortality in two growing rabbit flocks consisting of 5200 rabbits. Treatment: 1. sulphagunoxalin 2. Gallimycin 3. Sigmamycin 4. ESB_3

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