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STUDIES IN CHEMOTHERAPY

VIII. Some Toxic Effects of Repeated Administration of Sulfanilamide and Sulfanilyl Sulfanilamide ("Di-sulfanilamide") to Rabbits and Chickens [1]

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The toxicity of sulfanilamide for various species of animals has recently been investigated by Halpern and Mayer (*1*) and by Marshall, Cutting, and Emerson (*2*). Sulfanilyl sulfanilamide [2] ("di-sulfanilamide") was shown in this laboratory (*3*) to possess a low toxicity for mice and rats; similar findings have been reported by Barlow (*4*) and Domagk (*5*). However, the occurrence of peripheral neuritis in humans following the use of sulfanilyl sulfanilamide (*3*) (*6*) led us to investigate the problem of cumulative and of delayed effects from this compound, and also from sulfanilamide itself. Recently other cases of peripheral neuritis in man from the use of sulfanilyl sulfanilamide have been reported by Wigton and Johnson (*7*). The dimethyl derivative ("uliron") and also the monomethyl derivative of this compound have been used clinically, and peripheral neuritis from their use has been reported by Hüllstrung and Krause (*8*), Euler (*9*), Lemke (*10*), Tietze (*11*),[3] and in this country by Bannick, Brown, and Foster (*12*). Hüllstrung and Krause have produced emaciation and motor weakness in pigeons by oral administration of the methyl derivatives of sulfanilyl sulfanilamide.

[1] Revision of a paper presented before the American Society for Pharmacology and Experimental Therapeutics, Baltimore, Apr. 1, 1938.

The preceding papers of the series are as follows:

I. The action of sodium formaldehyde sulphoxylate in bacterial infections. By Sanford M. Rosenthal. Public Health Rep., 49: 908 (1934). (Reprint No. 1638.)

II. Chemotherapy of experimental pneumococcus infections. By Sanford M. Rosenthal. Public Health Rep., 52: 48 (1937). (Reprint No. 1796.)

III. The effect of p-aminobenzene sulphonamide on pneumococci *in vitro*. By Sanford M. Rosenthal. Public Health Rep., 52: 192 (1937). (Reprint No. 1802.)

IV. Comparative studies of sulphonamide compounds in experimental pneumococcus, streptococcus, and meningococcus infections. By Sanford M. Rosenthal, Hugo Bauer, and Sara E. Branham. Pub, Health Rep., 52: 662 (1937). (Reprint No. 1825.)

V. Sulphanilamide, serum, and combined drug and serum therapy in experimental meningococcus and pneumococcus infections in mice. By Sara E. Branham and Sanford M. Rosenthal. Public Health Rep., 52: 685 (1937). (Reprint No. 1826.)

VI. The chemotherapy of choriomeningitis virus infection in mice with sulphonamide compounds. By Sanford M. Rosenthal, Jerald G. Wooley, and Hugo Bauer. Public Health Rep., 52: 1211 (1937). (Reprint No. 1854.)

VII. Some new sulfur compounds active against bacterial infections. By Hugo Bauer and Sanford M. Rosenthal. Public Health Rep., 53: 40 (1938). (Reprint No. 1898.)

[2] Originally called di-sulfanilamide by us, the term sulfanilyl sulfanilamide has been adopted for this compound (Crossley, M. L., Northey, E. H., and Hultquist, M. E.: J. Am. Chem. Soc., 60: 2222 (1938)).

[3] See also Freusberg (Deutsch. Med. Wchnschr., 64:776 (1938)), Löhe (Med. Klin., 34:11 (1938)), and van Valkenburg (Lancet, 2:889 (1938)).

EXPERIMENTAL METHOD

All drugs were administered orally in these experiments. Adult rabbits were given 10 to 20 percent suspensions of the drugs in 2.5 to 5 percent acacia through a stomach tube. The drugs were administered to hens in gelatin capsules of 0.5 to 1.0 gm capacity, placed in the back of the throat with the forefinger and washed down with a little water. The diet of the rabbits consisted of oats and cabbage. In those experiments designed to study some effects of diet on toxicity, the animals were placed on oats alone or cabbage alone 2 to 4 weeks prior to the administration of the drugs. The hens were fed a commercial chicken feed composed of cracked corn, 70 percent, wheat, 15 percent, oats or barley, 10 percent, sorghum, 2.5 percent, Kaffir corn, 1.25 percent, and sunflower seed, 1.25 percent.

SULFANILAMIDE TOXICITY TO RABBITS ON OATS–CABBAGE DIET

The acutely fatal dose by mouth of sulfanilamide for rabbits has been reported as 2.0 to 2.5 gm per kilogram of body weight (Halpern and Mayer (*1*), Marshall (*2*), Raiziss (*13*), Hawking (*14*)).

In this study we were especially concerned with the effects of repeated administration. Single doses of 0.5 and 1.0 gm per kilo of sulfanilamide caused transitory ataxia in some cases but no fatalities with the exception of rabbit No. 790 (table 2). This animal was to receive a second dose, but because of his appearance this was withheld. The repeated administration of 0.5 to 1.0 gm per kilo resulted in a high mortality (tables 1, 2, and 3). The majority of rabbits became ataxic and spastic, and before death appeared moribund, although they responded to sensory stimulation. Dyspnea was observed as a late symptom. Rabbits Nos. 791 and 793 showed no acute nervous symptoms, but progressive emaciation and weakness led to death in 7 and 19 days, respectively. Delayed deaths in rabbits similar to these were also encountered in subsequent experiments; in the absence of characteristic pathological findings the exact role of the drug in these cases remains to be established.

One-half gram per kilo of sulfanilamide was administered daily for 9 to 10 days to 5 rabbits. After several doses, spasticity, ataxia, and weight loss were manifested by 4 of them, all of which later succumbed (table 3). The fifth animal showed no acute symptoms and remained well.

TABLE 1.—*The absence of effects of single doses of 0.5 to 1.0 gm per kilo of sulfanilamide given orally to rabbits on a diet of oats and cabbage*

Rabbit number	Single dose of sulfanilamide (gm per kilo)	Effects	Rabbit number	Single dose of sulfanilamide (gm per kilo)	Effects
814	0.5	None.	818	1.0	None.
816		Do.	820		Do.
817		Do.	823		Do.
828		Do.	824		Do.
833		Do.	826		No acute symptoms.

TABLE 2.—*Toxicity of repeated oral administration of 0.5 to 1.0 gm per kilo of sulfanilamide to rabbits on an oats and cabbage diet*

Rabbit number	Sulfanilamide, daily dosage		Effects
	Grams per kilo	Number of days	
779	1	2	Ataxic, spastic, head hangs, moribund, death on 4th day.
791	1	2	Weakness, emaciation, no ataxia. Death on 9th day.
792	1	2	On 3d day moribund, lies on side, response to stimulation, death on 4th day.
793	1	2	Gradual emaciation, no nervous symptoms, death on 21st day.
794	1	2	Weak, ataxic, no spasticity, death on 3d day.
790	1	1	Ataxic, spastic, death on 2d day.
775	1	3	Ataxic, spastic, death on 6th day.
776	1	3	Head hangs, wobbly, does not walk, death on 11th day.
	0.5	6	
778	1	3	No acute symptoms, temporary weight loss. Found moribund
	0.5	9	in tetanic convulsions on 40th day.[1]
777	1	3	No symptoms, slight loss of weight, recovery.
	0.5	9	

[1] Death not attributed to drug therapy.

TABLE 3.—*Toxicity of 0.5 gm per kilo of sulfanilamide daily for 10 days to rabbits on an oats and cabbage diet*

Rabbit number	Sulfanilamide, daily dosage		Effects
	Grams per kilo	Number of days	
782	0.5	10	No symptoms, survived.
783	0.5	9	Moribund, lies on side, responds to stimulation. Marked loss of weight. Death on 10th day.
784	0.5	10	Spastic, ataxic, dyspneic, followed by emaciation and death on 26th day.
785	0.5	10	Some ataxia, emaciation, death on 15th day with cyanosis and dyspnea.
786	0.5	10	Weak, ataxic, loss of weight, death on 14th day.

SULFANILAMIDE TOXICITY TO RABBITS ON RESTRICTED DIETS

Experiments on rabbits were characterized by considerable variation in susceptibility to sulfanilamide; a few animals would remain symptom-free following doses that were fatal to other members of the same group. Experiments were carried out to investigate the role of diet as a possible cause of this variation. Rabbits were placed upon diets of oats alone and cabbage alone for 3 to 4 weeks prior to administration of sulfanilamide. Water was kept in the cages of animals given oats, but no additional water was supplied to the animals on the cabbage diet.

Nine rabbits on a cabbage diet were given 0.5 gm per kilo of sulfanilamide daily for 8 to 10 days. With the exception of occasional ataxia, no symptoms and no fatalities occurred in this group (fig. 1).

Fifteen rabbits on an oat diet were given 0.5 gm of sulfanilamide daily for 7 to 9 days. All animals succumbed during or shortly after the treatment (fig. 2).

The explanation of this relation of diet to toxicity must await further work. That it is not simply a question of dietary deficiency is suggested by the experiments in which this drug was more toxic with a diet of oats plus cabbage than with cabbage alone. The experiments are reported at this time to emphasize the fact that dietary factors must be considered in future studies of the toxicity of sulfanilamide.

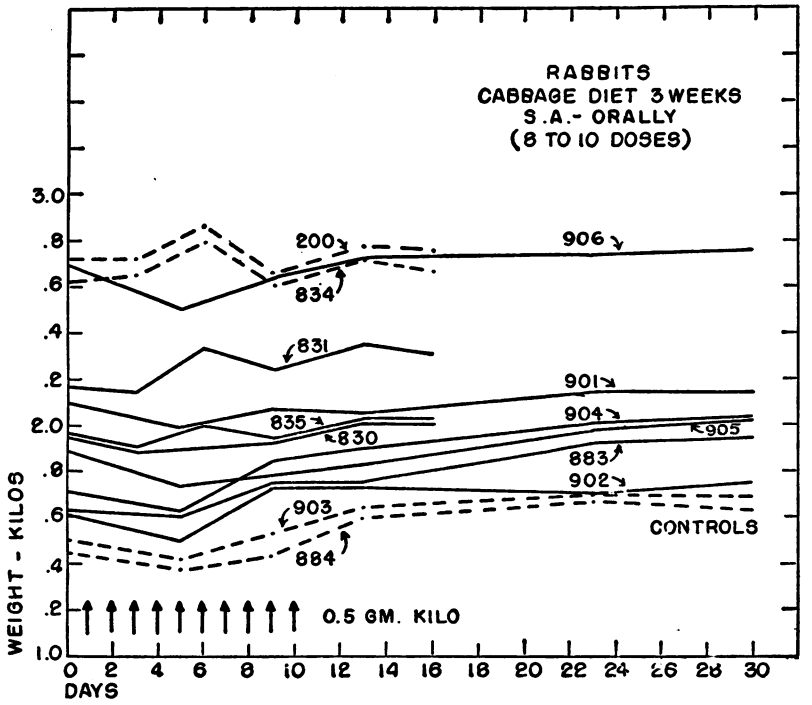

FIGURE 1.—0.5 gm per kilo of sulfanilamide for 8 to 10 doses is tolerated by rabbits kept on a cabbage diet for 3 weeks prior to the experiment. Dotted lines represent control animals.

TOXICITY OF SULFANILAMIDE TO CHICKENS

Repeated oral administration of sulfanilamide to adult hens led to an intoxication characterized first by drowsiness, listlessness, and a tendency to sit, later followed by spasticity, wobbly gait, weakness, particularly marked in the legs, and progressive emaciation. In many cases these symptoms continued after the cessation of therapy and often led to death. The affected hens showed difficulty in standing or walking even though motor power in their wings, as shown by their ability to fly, appeared good. It is possible, however, that the motor symptoms were simply a manifestation of general weakness;

in the absence in many cases of definite pathological changes, we cannot pronounce this condition a peripheral neuritis, although the appearance of many of the hens was suggestive of this condition.

In our earlier experiments, symptoms were produced in some hens with a total of 1 to 2 gm per kilo of sulfanilamide. Since the possibility was considered that fowl paralysis might have been endemic among our chickens, we have attempted to exclude this complication

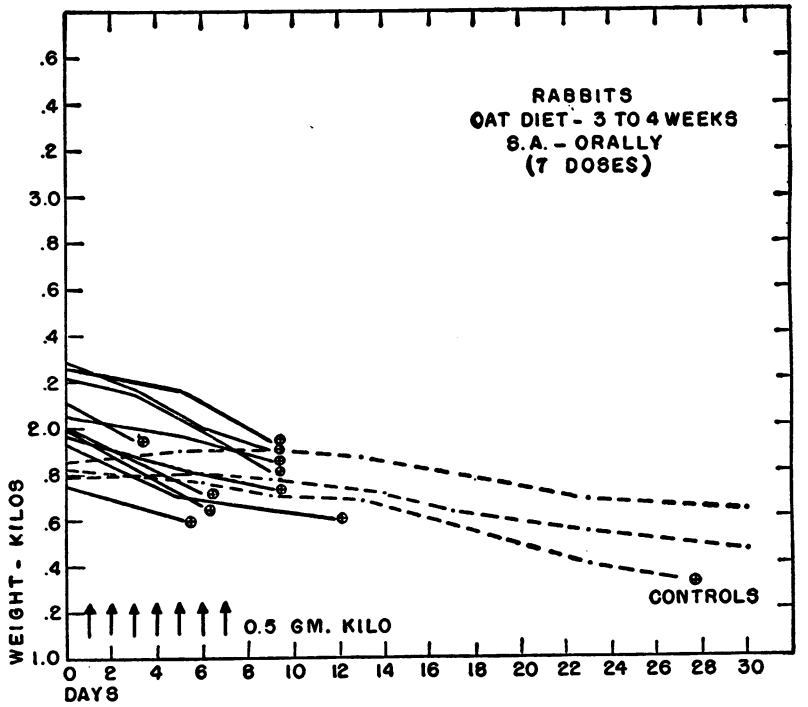

FIGURE 2.—0.5 gm per kilo of sulfanilamide for 7 doses is fatal to rabbits kept on a diet of oats alone for 3 to 4 weeks prior to the experiment. Circular mark signifies death of animal. Five additional treated rabbits behaved similarly.

by keeping the animals under observation for 1 to 3 months before the experiment, by employing a suitable number of control hens kept in the same cages, and by careful pathological examinations at the termination of the experiments. No evidence was obtained that fowl paralysis was present among these hens.

Eight hens were given 2 daily doses of 1.0 gm per kilo of sulfanilamide. Eight hens were kept with them as controls. No symptoms were observed except a temporary weight loss in the treated animals (fig. 3).

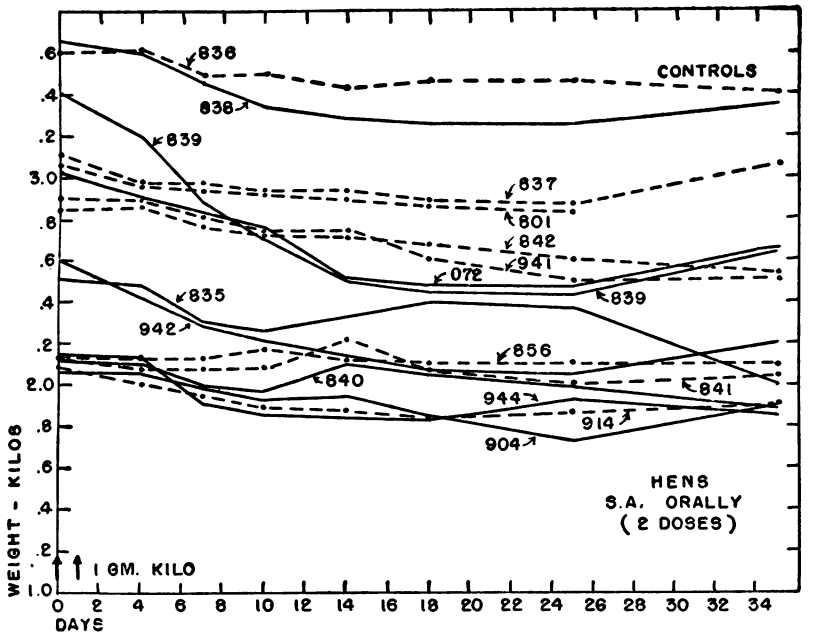

FIGURE 3.—Two daily doses of 1.0 gm per kilo of sulfanilamide caused only temporary weight loss to chickens.

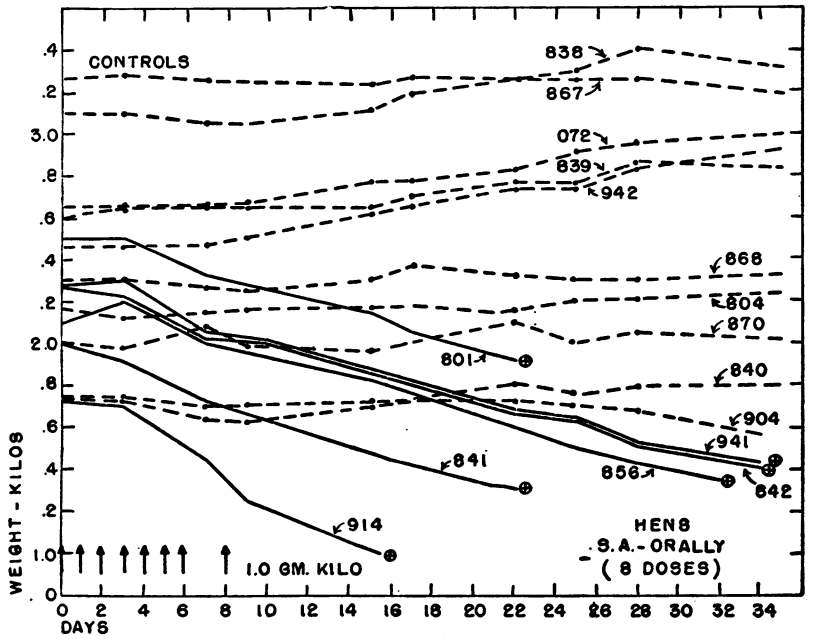

FIGURE 4.—Eight daily doses of 1.0 gm per kilo of sulfanilamide to chickens caused progressive loss of weight, weakness, particularly marked in the legs, and delayed death.

In another group of hens, 6 were given 8 daily doses of 0.5 gm per kilo and 6 were given 8 daily doses of 1.0 gm per kilo (figs. 4 and 5). Ten hens were kept in the same cages as controls. All treated animals showed progressive emaciation and neuromuscular weakness and succumbed within 1 to 4 weeks after the last dose. The control animals remained free from symptoms.

THE TOXICITY OF SULFANILYL SULFANILAMIDE [4] ("DI-SULFANILAMIDE") TO RABBITS

Mixed diet.—Single oral doses of 1 and 2 gm of sulfanilyl sulfanilamide ("di-sulfanilamide") per kilo to each of 5 rabbits produced no symptoms and no weight loss, with the exception of one rabbit which developed marked diarrhea and died on the third day.

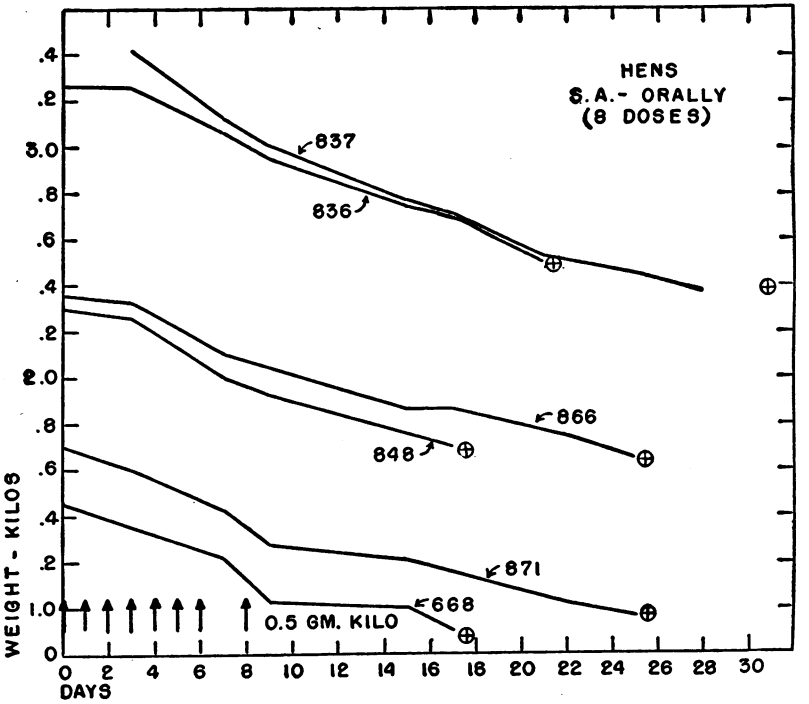

FIGURE 5.—Results similar to those seen in figure 4 from 8 doses of 0.5 gm per kilo of sulfanilamide to chickens.

Ten rabbits received 1 gm per kilo daily for 6 to 8 days (table 4). Weight loss occurred in only 3 animals. Six of the 10 rabbits died between the 7th and 13th day. Some of them exhibited symptoms similar to those observed with sulfanilamide—weakness, ataxia, spasticity, ending in a moribund condition. In others spasticity and ataxia were not observed. Dyspnea was often noted as a late symptom. Four of the 10 rabbits survived this therapy without symptoms except for temporary weight loss in one.

[4] Obtained from Merck and Co., Dermatological Research Co., and Winthrop Chemical Co.

TABLE 4.—*Toxicity of 1 gm per kilo orally of sulfanilyl sulfanilamide ("di-sulfanilamide") daily for 6 to 8 doses. Oats and cabbage diet*

Rabbit number	Sulfanilyl sulfanilamide, daily dosage		Effects
	Grams per kilo	Number of days	
747	1	8	Weakness, dyspnea, death on 10th day.
749	1	8	Weakness, dyspnea, ending in muscular paralysis, death on 13th day.
751	1	8	Dyspnea, ataxia, paralysis more marked in hind legs, death on 11th day.
752	1	8	Dyspnea, paralysis, death on 8th day.
767	1	6	Ataxic, spastic, dyspneic, death on 7th day.
768	1	6	Ataxic, hind legs spastic, dyspneic, death on 9th day.
750	1	8	No symptoms, slight weight loss, survived.
748	1	8	No symptoms, no weight loss, survived.
765	1	7	Do.
766	1	7	Do.

TABLE 5.—*Toxicity of sulfanilyl sulfanilamide ("di-sulfanilamide") to rabbits on diets of oats alone and cabbage alone*

Rabbit number	Sulfanilyl sulfanilamide, daily dosage		Effects
	Grams per kilo	Number of days	
Oat diet for 3 weeks			
748	1	5	Dyspnea, ataxia, no spasticity, weakness. Moribund 5th day. Death 6th day.
750	1	7	Weakness, dyspnea. Death 8th day.
766	1	9	No symptoms observed. Little weight loss. Died during night, 10th day.
782	1	4	Increasing weakness. Death on 5th day.
819	1	6	Spasticity, ataxia, weakness. Death on 7th day.
827	No drug		No symptoms for 1 month.
777	do		Do.
Cabbage diet for 3 weeks			
781	1	7	Weakness, diarrhea. Death on 7th day.
816	1	6	Do.
818	1	9	Weak, ataxic on 13th day. Death 15th day.
823	1	5	Weak, ataxic. Diarrhea. Death 6th day.
824	1	4	No symptoms except diarrhea. Found dead 5th day.
200	No drug		No symptoms for 1 month.
834	do		Do.

Restricted diets.—Five rabbits each on a diet of oats and on a diet of cabbage were given 1 gm per kilo of sulfanilyl sulfanilamide daily up to 8 doses. This compound behaved differently from sulfanilamide in that no differences in toxicity were observed in the two groups (table 5). All animals died during or shortly after the completion of therapy. Among the animals on a cabbage diet, diarrhea occurred in 4 receiving drug therapy. Spasticity was noted in only one rabbit on the oats diet and in none on the cabbage diet. In both experiments with restricted diets the drug was slightly more toxic than with the mixed diet.

TOXICITY OF SULFANILYL SULFANILAMIDE TO HENS

Single doses of 1 and 2 gm of sulfanilyl sulfanilamide per kilo to 4 hens each produced no symptoms.

Six hens received 0.75 to 1.0 gm per kilo daily for 6 to 9 days (table 6). Four died within 8 to 25 days with symptoms of weakness and emaciation. The two survivors showed leg weakness, curling of the toes on exertion, and a "stepping gait" that persisted for 3 months.

TABLE 6.—*Sulfanilyl sulfanilamide ("di-sulfanilamide") administered daily to chickens*

Hen number	Sulfanilyl sulfanilamide, daily dosage		Effects
	Grams per kilo	Number of days	
763	1.0	9	In 2d week partial paralysis of hind legs; unsteady gait, leg weakness, toes curl on exertion, atrophy of leg muscles present after 2 months. Good power in wings. Survived.
754	0.9	9	Similar to hen 763. Survived.
755	0.75	9	Leg paralysis, diarrhea, death in 15 days.
756	1.0	6	Death, 8th day.
757	0.9	6	Do.
758	0.9	6	Motor weakness of legs after 2 weeks, death in 25 days.

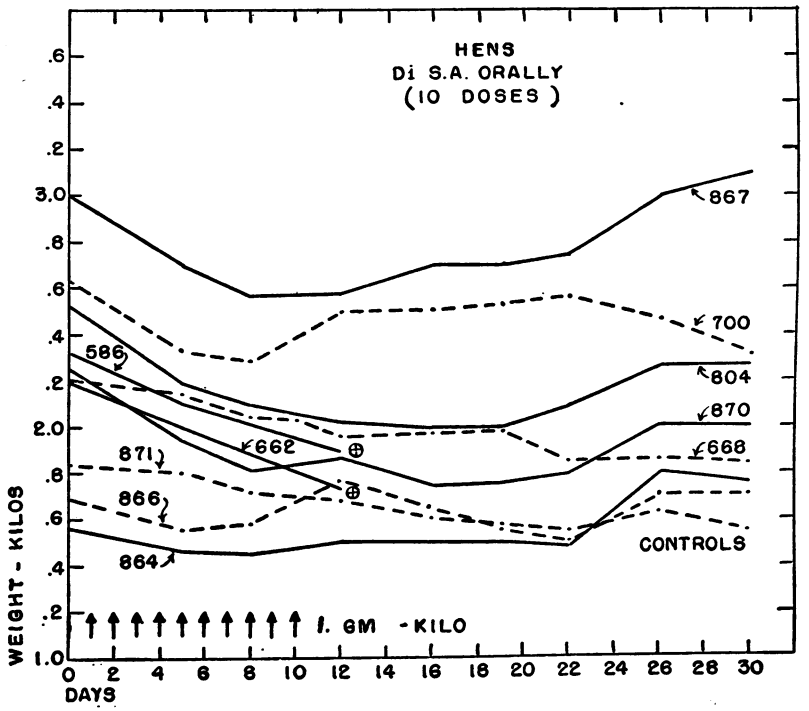

FIGURE 6.—Sulfanilyl sulfanilamide caused loss of weight and death in 2 of 6 chickens receiving 1.0 gm per kilo for 10 days.

An additional group of 6 hens received 1 gm per kilo for 10 doses. Two died on the twelfth day, following progressive weakness and emaciation. The remaining animals showed no symptoms other than temporary loss of weight (fig. 6).

It is evident that, as in the case of rabbits on a mixed diet, marked variations in susceptibility to sulfanilyl sulfanilamide occur among individual hens in the same group. The basis for this variability remains to be investigated.

DISCUSSION

It has previously been considered that the acute toxic action of sulfanilamide upon animals is completely reversible, and that animals surviving the immediate effects of the drug recover completely. It is, therefore, of interest that, in certain species of animals, delayed toxic manifestations characterized by emaciation and neuromuscular symptoms may occur. It is also of interest that in both rabbits and chickens evidence of a cumulative toxicity has been obtained. Published work indicates that such actions are not demonstrable in mice, rats, or dogs, although in the report of Marshall (*2*) one dog died after 72 daily doses of 0.2 gm per kilo, during which time marked loss of weight occurred. Halpern and Mayer (*1*) demonstrated a cumulative toxicity in guinea pigs, and this was also noted by Rich (*15*).

We have as yet no explanation as to the mechanism of the delayed toxic effects. Pathological studies have been carried out by Dr. A. A. Nelson, of this institute.[5] The histopathological changes varied with the type of animal and the nature of the drug it received. Hens in general showed marked changes; rabbits treated with sulfanilyl sulfanilamide showed moderate changes, while rabbits given sulfanilamide showed relatively slight lesions. As in the case of rabbits, chickens also showed considerable variation in susceptibility to sulfanilamide and sulfanilyl sulfanilamide. We have as yet carried out no investigations upon the influence of dietary or other factors upon the toxicity of these drugs to chickens.

In view of the frequency of production of polyneuritis in humans from sulfanilyl sulfanilamide and the rarity of this complication following sulfanilamide therapy, we had hoped to reproduce an animal counterpart of this specificity of action. However, while some differences in symptomatology were observed, the similarity of action of these two drugs in rabbits and chickens does not afford any basis for differentiation of their toxic effects as seen in humans.

There are many points of similarity between the toxic manifestations of these drugs in rabbits and chickens and those produced by triorthocresyl phosphate as described by Smith (*16*). There is also a resemblance between the polyneuritis in humans produced by sulfanilyl sulfanilamide and by triorthocresyl phosphate.

[5] To be published in the Public Health Reports.

SUMMARY

Sulfanilamide has been shown to possess a cumulative toxicity in rabbits. Repeated oral administration of 0.5 to 1.0 gm per kilo led to nervous symptoms, weakness, emaciation, and a considerable percentage of deaths.

The influence of diet was shown, in that a dosage of the drug which was tolerated by rabbits on a cabbage diet caused a high percentage of deaths in animals on a diet of oats plus cabbage or oats alone.

The daily oral administration of sulfanilamide to hens in doses of 0.5 to 1.0 gm per kilo for 10 days produced neuromuscular weakness and emaciation. Death frequently occurred and was often delayed for 1 to 4 weeks subsequent to the therapy. The appearance of many of these hens suggested peripheral neuritis, but in many of the animals it was not possible to establish this condition on a pathological basis.

Repeated daily administration of sulfanilyl sulfanilamide ("disulfanilamide") to rabbits and chickens also produced cumulative and delayed toxic effects. The drug was somewhat less toxic than sulfanilamide, and results in rabbits also differed in that no differences in mortality were observed between animals on oat and on cabbage diets.

The need for the use of several species of animals kept under controlled conditions, in the study of toxicity, is again emphasized by these results. It is also clear that toxicity studies of a drug by single dosage may give no true indication of results from repeated administration. The delayed toxic effects from sulfanilamide as seen in chickens must at present be given no clinical implications, because of the relatively large doses we have employed, and because no similar effects have to our knowledge been reported to occur in man following its use.[6] The extent to which cumulative toxicity of sulfanilamide occurs in man remains to be determined, particularly under those conditions often present during therapy—restriction of diet and toxemia.

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[6] Since this was written one case of peripheral neuritis has been reported by Ornsteen and Furst (J. Am. Med. Assoc., 111:2103 (1938)).

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HISTOPATHOLOGICAL CHANGES IN HENS AND RABBITS FOLLOWING ADMINISTRATION OF SULFANILAMIDE AND SULFANILYL SULFANILAMIDE (DI-SULFANILAMIDE)[1]

By A. A. NELSON, *Associate Medical Pathologist, United States Public Health Service*

In the course of Rosenthal's (*1*) studies on chemotherapy, histopathologic studies were made on 61 animals, intoxicated with sulfanilamide or sulfanilyl sulfanilamide, which had died or had been killed *in extremis* so as to obtain better preservation of tissues. The drugs were given orally. Daily dosage, time of death, etc., are given in tables 1 and 3. The tissues were fixed in 10 percent formalin and submitted to the writer for study. Paraffin sections were stained routinely by a hematoxylin-Romanowsky technique and by picrofuchsin. Weigert's myelin stain and Marchi's method for detection of myelin degeneration were also used on nervous tissues, and Perls' acid ferrocyanide reaction was used for demonstration of ferruginous pigment. Sudan IV, Nile blue sulfate, and polarized light were used on frozen sections for identification of fats; when the expression "fat free" is used in the text, it means that all these methods gave negative results. In the various tables, "0" means normal or essentially so, "+" means slight or few, "++" means moderate degree or number,

[1] From the Division of Pathology, National Institute of Health.

"+++" means marked or many, and "++++" means very marked to extreme in degree or number.

The cumulative fatal dosage of sulfanilamide was quite variable, and in general higher for rabbits than for hens. With sulfanilyl sulfanilamide fatal dosage was more uniform.

PREVIOUSLY REPORTED HISTOPATHOLOGICAL CHANGES FOLLOWING ADMINISTRATION OF SULFANILAMIDE AND RELATED COMPOUNDS

To date only fragmentary reports exist concerning the histopathological changes following administration of sulfanilamide and related compounds. Reports of clinically observable toxic reactions in human beings are fairly numerous (*2*, *3*). The histopathological findings are herewith summarized.

Geiling and Cannon (*4*) gave sulfanilamide to rats, rabbits, and dogs in doses of 0.2 gram per kilo thrice daily for a total of 8 or more doses without fatalities; some animals had convulsions but none had anuria. There was moderate fatty degeneration of some of the renal collecting tubules in dogs, and a lesser degree of the same change in rats; the livers of both showed no hydropic degeneration and practically no fatty degeneration.

Hawking (*5*) gave 10 rabbits intraperitoneal injections of 0.4 to 2.0 grams per kilo of p-amino-benzenesulfonamide (sulfanilamide); with the latter dose, symptoms began in ½ to 1 hour, consisting of retraction of the head, extension of legs, and dilatation of pupils; recovery began in 10 hours and the animals were well after 2 or 3 days. The surviving animals were killed after 1 week; the liver, kidneys, and other viscera showed no changes due to the sulfanilamide. In three animals dying from the drug, there were degenerative changes such as chromatolysis in the neurons of the anterior column of the spinal cord, and in some of the nerve cells of the cortex and midbrain.

Hageman (*6*) gave 15 Swiss mice sulfanilamide in doses of 1 to 2.5 grams per kilo per day for 1 to 14 days, both intraperitoneally and subcutaneously. It was not tolerated well in large doses and produced unsteadiness, incoordination, paralysis, acute anterior flexion of the spine, spastic extension of the legs, prostration, convulsions, and death; with smaller doses the symptoms were transient. Microscopic examination of the liver and kidneys showed no definite changes. The spleen showed a hemosiderosis roughly proportional to the total dose and to the duration of life after exposure, suggesting that the reaction was progressive after the drug was discontinued. A considerably greater incidence of eosinophils was found in the bone marrow of exposed animals than in that of controls; no other differences were noted, and the femoral and vertebral marrows were alike. Blood counts were not done. The intraperitoneal injection of sulfanilamide in saline gave a fibroblastic foreign body reaction, with milky white

spots on the peritoneal surfaces and crystals scattered through the area of reaction.

Marshall, Cutting, and Emerson (*7*) gave two dogs daily doses of 0.2 grams per kilo of sulfanilamide for 128 and 72 days, respectively. Sections of liver, kidney, spleen, heart, lung, bone marrow, and adrenal of both dogs were normal on microscopic examination. A group of six young rats was given 0.25 percent (0.16 to 0.35 grams per kilo per day) of sulfanilamide in their diet; after about 65 days these animals and a littermate control group were killed and the organs (liver, kidney, spleen, heart, adrenal, thyroid, intestine, and bone marrow) were examined microscopically. The organs of the treated animals were essentially normal, while in the control group many of the liver and kidney sections showed areas of hemorrhagic necrosis. The growth curves of both series were practically identical. The experiment was repeated using 0.75 percent (0.46 to 1.02 grams per kilo per day) of sulfanilamide in the diet. After about 70 days the weights of the treated animals were somewhat below those of the controls. On microscopic examination the various organs (liver, kidney, spleen, heart, testis, ovary, adrenal, thyroid, and bone marrow) of both treated and control groups were normal. In conclusion, Marshall, Cutting, and Emerson say: "A study of the acute toxicity of sulfanilamide has been made on mice, rabbits, and dogs. The toxicity of the drug for these animals appears to be relatively small, but the substance is not devoid of toxicity. Limited experiments on dogs and rats have shown no signs of chronic toxicity and no pathologic lesions in these animals after prolonged administration of sulfanilamide."

Hüllstrung and Krause (*8*) gave D. B. 87 (monomethyl sulfanilyl sulfanilamide) to a number of pigeons; the birds developed paralyses of the leg and wing muscles, became emaciated, and died. On microscopic examination, however, the peripheral nerves, spinal cord, and muscles of the extremities were negative. Animals treated with uliron (the dimethyl derivative of sulfanilyl sulfanilamide) did not develop these symptoms.

Kolmer, Brown, and Rule (*9*) stated that rabbits (number not given) had lived indefinitely following 10 daily subcutaneous injections of 0.004 to as much as 0.160 grams per kilo of sulfanilamide (each dose given in two portions 6 hours apart). The animals were then sacrificed and the heart, lungs, adrenals, spleen, liver, and kidneys examined histologically; the first four organs showed no histologic evidences of injury; the kidney of a rabbit receiving the heaviest dose showed slight degrees of cloudy swelling of the epithelium of the straight tubules, and the liver of a similar rabbit showed marked cloudy swelling of the lobular epithelium, particularly around the central veins. By oral administration the maximum tolerated dose was between 0.2 and 1.0 grams per kilo daily, divided into two portions

6 hours apart. Two rabbits died after being given 1.0 and 2.0 grams orally per kilo after 8 and 4 days, respectively. The heart, lungs, adrenals, spleen, liver, and kidneys were examined histologically in both the animals which had survived the oral dosage and in the two which had died from it. The heart, lungs, adrenals, and spleen showed no histologic evidences of injury. The kidneys of the two rabbits which succumbed showed slight degrees of cloudy swelling of the straight tubules. The liver of the rabbit given three daily doses of 2.0 grams orally showed marked cloudy swelling of the lobular epithelium, particularly around the central veins. Kolmer, Brown, and Rule stated that these results were essentially negative and confirmatory of the remarkably low toxicity of sulfanilamide; they were not at all sure that the histologic changes found had been produced by sulfanilamide, since they had been found in control rabbits and those subjected to streptococcus infection.

Cline (*13*) reports, with autopsy findings, a case of acute yellow atrophy of the liver following sulfanilamide medication.

Jaubert and Motz (*14*) found decreased numbers of spermatozoa in 23 gonorrheal patients treated with sulfanilamide compared with patients treated by older methods. On the other hand, Levaditi and Vaisman (*15*) found that sulfanilamide had no inhibiting effect on spermatogenesis in adult rabbits and mice; in growing mice, sulfanilamide in doses of 0.5 gram per kilo for 19 doses caused, after 56 days, retarded body growth and decreased numbers of spermatozoa on puncture of the epididymis. On histological examination they could not make out a damage to spermatogenesis.

PATHOLOGICAL CHANGES IN 21 RABBITS TREATED WITH FATAL DOSES OF SULFANILAMIDE (TABLE 1)

Lung.—The lung was examined in 19 animals and was normal in 13 of these. Three lungs showed pneumonic changes, one a moderate degree of bronchopneumonia, another a slight degree of bronchopneumonia in a stage of delayed resolution, together with moderate atelectasis, and the third a slight degree of peribronchial interstitial pneumonia, together with slight congestion and focal atelectasis. One rabbit showed a marked pulmonary edema, one a slight edema together with moderate congestion and slight focal atelectasis and emphysema, one a slight edema together with a few alveolar hemorrhages, and one showed moderate congestion and a few alveolar hemorrhages.

Liver.—The liver was examined microscopically in 20 animals, and in 12 of these it was negative or essentially so. The livers of the 8 remaining animals showed slight to moderate changes as follows (some livers had more than one type of lesion): Slight fatty change,

TABLE 1.—*Partial list of pathological changes found in rabbits after ad*

SULFANILAMIDE

Pharmacology No.	Pathology No.	Dosage: Grams per kilo daily	Dosage: Days given	Dosage: Total dose, grams	Day of death	Lung: Pneumonia	Lung: Edema	Lung: Congestion	Lung: Alveolar hemorrhage	Liver: Fatty change	Liver: Atrophy	Liver: Vacuolar degeneration	Liver: Excess bile pigment	Liver: Coccidiosis	Spleen: Hemosiderosis	Spleen: Follicle reticular cells	Spleen: Follicle phagocytosis	Spleen: Splenitis	Spleen: Congestion
779	12780	1.0	2	2.0	4	+	0	0	0	0	0	+	0	0	+	0	0	0	0
775	12787	1.0	3	3.0	6	0	0	0	0	+	+	0	0	++	++	+	0	0	0
776	12803	(1)	9	6.0	11	0	0	0	0	0	0	+	0	0	++	0	0	0	0
794	12804	1.0	2	2.0	3	0	0	0	0	0	0	0	++	0	+	0	++	0	
783	12806	0.5	9	4.5	10	----	----	----	----	0	0	0	++	0	+	0	0	0	++
792	12807	1.0	2	2.0	4	0	0	0	0	0	0	0	0	++	0	+	+	0	++
785	12820	0.5	10	5.0	15	0	0	0	0	0	+	0	0	0	++	0	0	0	+
786	12821	0.5	10	5.0	14	0	0	++	+	0	+	0	++	0	++	0	0	0	
791	12831	1.0	2	2.0	9	----	----	----	----	0	+	+	0	0	+	+	0	0	0
793	12891	1.0	2	2.0	21	0	0	0	0	----	----	----	----	----	+	0	0	0	0
784	12892	0.5	10	5.0	26	0	0	0	0	0	0	0	+	0	++	+	0	0	0
778	12919	(1)	12	7.5	40	0	0	0	0	0	0	0	+	0	+	+	0	0	0
O 822	13295	0.5	3	1.5	3	+	0	+	0	0	0	++	0	0	+	+	++	0	0
C 765	13296	0.5	3	1.5	4	0	0	0	0	0	0	0	0	0	+	+	+	+	++
O 820	13322	0.5	6	3.0	7	0	0	0	0	0	0	0	0	0	++	0	++	0	0
O 828	13323	0.5	6	3.0	8	0	0	0	0	0	0	0	0	0	++	+	+	0	0
O 833	13324	0.5	7	3.5	7	0	0	0	+	0	0	0	0	0	+++	+	+	0	0
O 814	13333	0.5	10	5.0	10	++	0	0	0	0	0	0	0	0	++	0	0	0	0
O 891	13556	0.5	10	5.0	10	0	+	++	0	0	0	0	0	++	++	+	+	0	0
O 899	13557	0.5	9	4.5	10	0	+++	0	0	+	0	0	0	+	+	0	0	0	++
O 889	13612	0.5	10	5.0	14	0	0	0	0	0	0	0	0	0	+	0	0	0	0

SULFANILYL SULFANILAMIDE

752	12737	1.0	5	5.0	8	++	+	++	0	++	+	0	0	0	++	++	+	+	++
751	12738	1.0	5	5.0	11	++	0	0	0	0	+	0	++	0	++	+	+	0	0
749	12756	1.0	5	5.0	13	0	0	0	0	+	+	0	0	0	+	0	0	0	0
768	12766	1.0	6	6.0	9	----	----	----	----	++	+	0	++	0	+	+	+	0	0
767	12771	1.0	6	6.0	7	----	----	----	----	++	0	++	0	0	++	+	0	0	+++
829	12971	1.0	1	1.0	4	0	0	0	0	0	0	+	0	0	0	+	0	0	0
O 78[illegible]	13297	1.0	5	5.0	5	++	0	0	0	0	0	+	0	0	+++	+	0	0	0
O 823	13298	1.0	4	4.0	5	+++	0	0	0	0	+++	0	0	0	+++	+	0	0	0
O 824	13299	1.0	4	4.0	5	+++	0	0	0	0	++	0	0	0	++	++	+	0	+++
O 748	13319	1.0	5	5.0	6	0	0	0	0	0	++	0	0	0	+++	+	++	+	0
O 750	13320	1.0	7	7.0	8	0	0	0	0	0	0	0	0	0	+	+++	0	0	0
C 816	13321	1.0	6	6.0	7	0	0	0	0	0	0	0	0	0	+++	0	0	0	++
C 781	13325	1.0	6	6.0	6	++	0	0	0	0	0	0	0	0	+	+	0	0	+++
O 819	13326	1.0	6	6.0	6	+	++	0	0	0	0	0	0	0	++	++	+++	0	++++
O 818	13354	1.0	9	9.0	15	0	++	++	0	0	0	++	0	0	++	+	++	0	0

[1] 1.0 gram per kilo per day for 3 days, followed by 0.5 gram per kilo per day.
[2] Pigment.

ministration of fatal doses of sulfanilamide and sulfanilyl sulfanilamide

SULFANILAMIDE

Voluntary Muscle		Kidney								Testis			Epididymis		Bone Marrow		
Focal necrosis	Calcification	Tubular degeneration	Casts and debris	Tubular dilatation	Doubly refractile concretions	Spontaneous nephritis	Pigment or fat	Spontaneous encephalitis	Peripheral neuritis	Mature spermatozoa	Degenerating cells	Teratocytes	Degenerating epithelium	Tubular dilatation and debris	Hyperplasia	Hypoplasia	Pigment
+++	0	+++	+++	+	+	0	0	0	0	------	------	------	------	------	------	------	------
0	0	+	+	+	0	0	0	0	------	------	------	------	------	------	------	------	------
+++	+++	+	++	++	0	0	0	+	0	------	------	------	------	------	------	------	------
0	0	+	0	++	0	++	0	++	+	0	+	0	++	0	------	------	------
0	0	+	+	0	0	++	0	+++	0	++	++	0	+	0	------	------	------
+	0	+	0	+	0	0	0	+	0	[4] 0	0	0	0	0	------	------	------
------	------	++	+	+	0	0	0	+	------	------	------	------	------	------	------	------	------
+	+	+	+	0	0	++	0	+++	0	++	++	+	+++	0	------	------	------
++	0	+	+	++	++	+	0	+	0	+	+++	0	0	+++	+	0	0
------	------	+	0	0	0	0	0	0	0	0	0	+	++	++	0	+	++
0	0	+	0	0	0	0	[3] 0	+	0	------	------	------	------	------	0	0	0
0	0	+	0	0	0	0	[3] 0	------	------	0	0	0	0	0	0	0	0
0	0	+	0	0	0	0	[3] 0	+++	0	+++	++	+	0	0	++	0	0
------	------	------	------	------	------	------	------	------	0	++	0	+	0	0	0	0	0
------	------	------	------	------	------	------	------	+++	0	++	0	+	0	0	0	+	++
------	------	+	+	++	0	+	0	++	+	------	------	------	------	------	0	0	+
0	0	+	+	++	0	0	0	------	------	------	------	------	------	------	+	0	+
0	0	+	+	+	0	0	0	------	------	------	------	------	------	------	0	0	0
0	0	+	+	+	0	0	[3] 0	------	------	------	------	------	------	------	0	0	0
+++	++	+	+	+	0	0	[3] 0	------	------	------	------	------	------	------	++	0	0

SULFANILYL SULFANILAMIDE

0	0	++	++	++	++	0	0	0	+	------	------	------	------	------	------	------	------
------	------	++	++	++	++	0	0	------	------	------	------	------	------	------	------	------	------
0	0	++	++	++	++	0	0	+	0	------	------	------	------	------	------	------	------
0	0	++	+++	++	++	0	0	0	0	++	++	0	0	0	------	------	------
0	0	+	+++	+++	0	0	[3] 0	0	----	+++	0	0	0	0	------	------	------
0	0	++	+	0	0	0	[3] 0	0	0	------	------	------	------	------	------	------	------
0	0	0	+++	+++	0	0	0	++	+	++	++	+	0	0	0	0	0
0	0	0	+++	+	0	0	0	------	+	------	------	------	------	------	0	0	0
------	------	0	++	+	0	+	0	------	0	------	------	------	------	------	0	0	0
0	0	0	++	++	+++	+	0	------	0	+++	0	0	0	0	0	0	0
0	0	0	+	0	0	+	0	------	+	------	------	------	------	------	0	0	0
------	------	0	++	0	0	++	0	------	+	------	------	------	------	------	0	++	0
------	------	0	+	0	0	+	0	------	+	------	------	------	------	------	+	0	0
0	0	+	+++	++	++	+	0	------	+	------	------	------	------	------	0	+	+
0	0	++	++	++	+	+	0	------	0	------	------	------	------	------	0	0	0

[3] Fat.
[4] Immature testis.

two; slight diffuse atrophy, two (rabbits 775 and 786); slight central atrophy, two; vacuolar degeneration, mainly central, three slight and one moderate; coccidiosis (two in otherwise negative livers), four; slight or moderate excess of bile pigment, five. Special examination for fat was made of five livers; three were fat free; rabbit 899 showed small amounts of fat in both the hepatic and Kupffer cells, with no anisotropic material in the former and a moderate amount in the latter; rabbit 889 showed no fat in the hepatic cells and a small to moderate amount, with no anisotropic material, in the Kupffer cells.

Spleen.—The spleen was examined microscopically in all 21 rabbits. About the only significant finding was an excess of hemosiderin in some of the spleens (fig. 1). Hemosiderosis was graded 0 in 3, + in 10 (this degree appears to be within normal limits), ++ in 7, and +++ in 1. The hemosiderin was about equally distributed between the pulp and sinuses; only occasional granules were found within the follicle reticulum cells. Perls' reaction was done on at least three of these spleens to verify the hemosiderin nature of the intracellular brown pigment. The reticulum cells of the follicles were graded as inconspicuous in 11 and moderately prominent in 10; in one of the first group the pulp reticulum cells were somewhat hyperplastic. Phagocytic activity of the follicle reticulum cells was usually slight when present, and bore no particular relationship to the prominence of the reticulum cells. Splenitis of slight degree was noted in two cases; in rabbit 822 the infiltrate consisted of polymorphonuclear leucocytes and in rabbit 765 of these and plasma cells. Congestion of the sinuses of varying degrees was noted in six spleens, and slight erythrophagia in one (rabbit 889).

Kidney.—As in the lung, liver, and spleen, the changes in the kidney were rather slight in this group of animals. One or more of the changes of degeneration of the tubular epithelium, presence of casts, desquamated cells and debris in the tubules, and dilatation of the tubules were present in 18 of the 20 animals examined; with one exception (rabbit 779) they were slight or moderate in degree. The degenerative changes in the tubular epithelium were present chiefly in the convoluted tubules, while the tubular dilatation was seen chiefly in the collecting tubules.

The kidneys of rabbits 779 and 791 showed (in paraffin sections) peculiar doubly refractile radially striated crystalline bodies (fig. 2). These bodies were seen more frequently in the kidneys of rabbits receiving sulfanilyl sulfanilamide, but will be described at this point. The convoluted tubules and to a lesser extent the collecting tubules contained oval masses 10 to 40 micra in diameter, sometimes with the edges more or less squared off, and sometimes more or less fragmented; these masses uniformly showed a radial structure and were highly refractile under crossed Nicol prisms; sometimes a small granular

nuclear mass could be seen. The number of these structures varied from 1 to 20 per square millimeter in the same kidney. Occasionally one of them could be seen within or between the epithelial cells of a tubule, and gave the impression that it was increasing in size, and pushing apart the epithelial cells. We do not know the nature of these peculiar crystalline structures, and whether or not sulfanilamide is one of their components.

Five of the 20 kidneys in this group showed a slight to moderate degree of old scarring from spontaneous nephritis; this bore no relationship to the degree of the other changes observed. With fat stains three kidneys were fat free and one showed a moderate focal fatty change, but no anisotropic material, in the tubular epithelium, especially at the cortico-medullary junction; the remaining 16 kidneys showed no fatty change with the routine paraffin sections. One kidney showed a moderate and one a slight degree of focal fine greenish pigmentation of the convoluted tubular epithelium; only small proportions of this pigment were iron-containing. One kidney showed about one mitotic figure per square millimeter in the tubular epithelium; more will be said about this feature in connection with sulfanilyl sulfanilamide. The glomeruli in all the kidneys were essentially normal.

Brain.—The brain was examined in 15 animals. In general, sections were taken to include frontal, parietal, and temporal cortex, basal nuclei, thalamus, hippocampus, midbrain, pons, cerebellum, and medulla. In none of the 15 animals could definite lesions attributable to the experiment be made out; in rabbit 779 there were questionable changes in the ganglion cells of the parietal and temporal cortex and in the ascending nuclei of the fifth nerve, consisting of varying degrees of tigrolysis, peripheral segmentation of Nissl granules, and irregular staining of cytoplasm. Ten of the 15 brains showed slight to marked degrees of the spontaneous encephalitis of rabbits (see Jaffe (*10*) for description and illustrations); these lesions are commonly encountered in apparently normal rabbits and as far as we can determine are of no significance in this study.

Spinal cord.—The spinal cord was examined in 16 animals; from 1 to 3 levels of each cord were sectioned. In only one animal (rabbit 793) were there definite nerve cell changes; here a few anterior horn cells in the lumbar cord showed vacuolation and swelling of the cytoplasm, and chromatolysis. No degenerative changes in the nerve fibers could be made out. Lesions of spontaneous encephalitis were few in the cord as compared to the brain.

Peripheral nerves.—The sciatic nerve was examined in 15 animals. It was normal except in 3 animals, where occasional short segments of nerve fibers showed swelling, rarefaction, and the formation of balls or irregular masses of myelin staining black with the Marchi technique.

Gastrointestinal tract.—The small intestine was examined in 11 animals, the duodenum and colon in 4, the stomach in 2, and the sacculus robundus in 1. These sections were uniformly negative except for rabbit 784, in which a moderate number of coccidia were seen in the crypts of the small intestine.

Heart.—The heart was examined in 14 animals; all sections were negative; in 2 cases fat stains were done and the sections were fat free.

Voluntary muscle.—Sections of voluntary muscle from the thigh were made in 15 animals; 7 of these showed lesions, chiefly focal coagulation necrosis. Three showed this change to a marked degree (two with calcification), one moderately and two slightly (one with calcification); one animal showed slight atrophy of the muscle. The frequency of these changes would appear to be of significance, since in 11 rabbits treated with sulfanilyl sulfanilamide in which the same muscles were examined microscopically no lesions were found.

Pancreas.—This organ was examined in 13 animals and was negative in 12; in rabbit 786 about one-half of the island cells were somewhat shrunken and karyopyknotic, and a small percentage of the acinar cells showed similar changes.

Adrenal.—Examined in 15 animals and all negative.

Testis.—Six of the nine animals in which the testes were examined showed slight to marked damage, with reduction in numbers of mature spermatozoa, necrosis of spermatids and spermatocytes, presence of teratocytes in the testicular tubules, degenerative changes in the epithelium of the epididymal tubules (nuclear rarefaction, fragmentation, and the formation within or between the cells of cystic cavities up to 50 μ in diameter), and dilatation of the epididymal tubules and filling of them with macrophages, desquamated tubular cells, and debris. The testis of rabbit 792 was immature.

Bone marrow.—The femoral marrow was examined in 11 rabbits; in 3 it was considered normal. In the remaining 8 the changes were variable; 3 showed a slight or moderate hypoplasia and 5 a slight or moderate hyperplasia. Since in the adult rabbit (and to a lesser extent in the hen) the femoral marrow is more cellular at the periphery than in the center in the transverse plane, care was taken to make transverse sections through the entire diameter of the marrow as well as longitudinal sections. An example of a moderately hypoplastic marrow compared with the normal is shown in figure 3. The marrow fluctuations affected chiefly the granulocytes; with hypoplasia their number was reduced and with hyperplasia it was increased. In 3 of the 5 hyperplastic marrows the proportion of early to late myeloid forms appeared normal; in rabbit 765 the increase was chiefly in stem cells and early granulocytes; in rabbit 889 the more mature granulocytes were especially prominent. In one of the hypoplastic marrows (rabbit 793) the reduction affected chiefly the normoblasts. Small to

moderate amounts of brown intracellular pigment were present in four marrows, moderate nuclear fragmentation in rabbit 791 and considerable phagocytosis of granulocytes by megakaryocytes in rabbit 814.

Other organs.—The ovary was examined in rabbit 778, and a sympathetic ganglion in rabbit 822; both sections were negative.

SUMMARY

The pathological changes produced by the administration of fatal doses of sulfanilamide to a group of 21 rabbits were usually of slight to moderate degree, although in some cases they were marked. They consisted of renal changes (epithelial degeneration, casts and debris in tubules, and dilatation of tubules), splenic hemosiderosis, degenerative changes in the testis and voluntary muscles, and hypo- or hyperplasia of the bone marrow with changes in the cell proportions. Each of these changes was present in from one-third to two-thirds or more of the animals. Less frequent changes were bronchopneumonia or other pulmonary lesions, and fatty change or atrophy of the liver. Lesions in the central and peripheral nervous systems did not occur with enough frequency to warrant ascribing them to treatment with sulfanilamide, although the slight degree of peripheral neuritis found in 3 of 15 rabbits might be so considered.

PATHOLOGICAL CHANGES IN 15 RABBITS TREATED WITH FATAL DOSES OF SULFANILYL SULFANILAMIDE (TABLE 1)

Lung.—This was examined in 13 animals; 7 of these showed pneumonic changes, usually focal and presumably terminal; 6 were of moderate and 1 of slight degree. In four the exudate was alveolar in distribution, in two interstitial, and in one both. The exudate was predominantly polymorphonuclear except in rabbit 751, where it consisted of macrophages. Slight to moderate edema was noted three times, twice in association with pneumonia. Moderate congestion, focal atelectasis, and focal emphysema were each noted in 2 animals.

Liver.—The liver was examined in all 15 animals. Three livers showed moderate and one slight fatty change; in one of these the diagnosis was verified with fat stains. Four livers (three with fatty change) showed slight central atrophy. Vacuolation and other degenerative changes in the hepatic cells were noted six times; fat stains were done on the liver with the most marked vacuolation and it was fat free. Coccidiosis was found in two livers. In rabbit 829 there was a slight excess of bile pigment granules in the liver cells. The Kupffer cells of rabbit 767 contained a moderate excess of large dark pigment granules, about half of which were hemosiderin; the hepatic cells contained a small amount of similarly colored pigment, which was not hemosiderin. This same liver showed about 10 mitoses per square

millimeter among the hepatic cells, an unusual number for a rabbit liver, and the only liver in either series of rabbits to show a notable number of mitoses.

Spleen.—The spleen was examined in all 15 animals. Hemosiderosis was graded as 0 in 1, +in 4, ++ in 6, and +++ in 4. This is distinctly greater in degree than in the sulfanilamide-treated rabbits, and presumably indicates a greater degree of blood destruction. The distribution of the hemosiderin was the same as with sulfanilamide. The reticulum cells of the follicles were graded as inconspicuous in two, moderately prominent in nine, and prominent or very prominent in four. Phagocytic activity of the follicle reticulum cells was absent in seven, slight in five, and moderate or marked in three. These cells were in general more prominent and active in this group than in the previous one. Three spleens showed a slight polymorphonuclear leucocyte infiltration of the pulp, while in rabbit 816 numerous normoblasts were seen in the pulp and sinuses. Congestion of the pulp of moderate or marked degree was seen in three spleens; moderate congestion of the sinuses was seen in rabbit 816 and extreme congestion in rabbit 819. Slight sinus erythrophagia was noted in rabbits 751 and 768.

Kidney.—In the kidney, examined in all 15 animals, the lesions were quite marked, much more so than in the group treated with sulfanilamide. In general, there was slight to marked dilatation of the collecting tubules (11 animals), small to large amounts of hyaline casts, cells and debris in the tubules (14 animals), and slight to moderate degrees of degenerative changes such as vacuolation and hyaline droplet formation in the convoluted tubule epithelium (8 animals). Seven kidneys contained the peculiar doubly refractile concretions described previously. Five kidneys showed a slight and one a moderate degree of old spontaneous nephritis; as in the other group of rabbits there was no relation between these and the recent lesions. In the kidney of rabbit 767 there were about 10 mitoses per square millimeter in the tubular epithelium; there were an equal number of mitoses in the liver of this same rabbit. Other rabbits showing mitoses were rabbit 752 (2 to 3 per sq. mm. in the kidney and 1 to 2 in the adrenal) and rabbit 776 (sulfanilamide series; 1 mitosis per sq. mm. in the kidney). The kidney of rabbit 767 was slightly edematous, contained no ferruginous pigment, and contained a small amount of fat in fine droplets in the tubular epithelium. The renal pyramid in rabbit 823 contained several small chronic abscesses, which were thought to bear no relation to the experiment. The glomeruli were essentially negative in all the animals. The dilatation of the collecting tubules (fig. 4) is a peculiar lesion; it has not been noted in previous series of experimental rabbits and no theory as to its causation is advanced.

Brain and spinal cord.—This was examined in six animals and was negative in all as far as lesions attributable to the sulfanilyl sulfanilamide were concerned. Rabbit 749 showed a slight and rabbit 782 a moderate degree of spontaneous encephalitis. The spinal cord showed no lesions in the four animals in which it was examined.

Peripheral nerves.—The sciatic nerve was examined in 13 animals; in 8 of these, small numbers of segments of nerve fibers were rarefied, swollen, and with osmic acid showed blackened balls and fragments of myelin. None of these lesions was marked in degree (about 1 or 2 percent of the total mass of nerve was involved), and although we believe that they are of significance, this is not beyond question. However, it is of interest that in the sulfanilyl sulfanilamide group 8 of 13 (62 percent) showed this mild peripheral neuritis, while only 3 in 15 (20 percent) of the sulfanilamide group had it. It is also of interest that in human beings the incidence of clinical peripheral neuritis is greater with sulfanilyl sulfanilamide than with sulfanilamide.

Gastrointestinal tract.—Sections were made of the small intestine in seven animals, of the stomach in two, and of the duodenum in one; all were negative.

Heart.—Eleven of the twelve hearts examined were negative. The myocardium of rabbit 782 showed numerous short segments with changes grading from hydrops to coagulation necrosis, with no cellular reaction; fat stains showed small to large amounts of fat, with no anisotropic material.

Voluntary muscle.—Sections of voluntary muscle from the thigh were negative in all 11 animals examined; this is in contrast to the sulfanilamide series, where 7 of the 15 muscles showed varying, usually quite marked, degrees of focal coagulation necrosis, with or without calcification.

Pancreas.—Examined in nine animals; all negative.

Adrenal.—Sections of the adrenal were made in 11 animals. All were negative except for the presence of one to two mitoses per square millimeter in rabbit 752, and focal congestion in rabbit 748.

Testis.—Examined in four animals; two were negative or essentially so; the other two showed moderate numbers of degenerated seminiferous cells. Some of the epididymal tubules of rabbit 767 contained numerous macrophages. While not enough testes were examined in this series to make a positive statement, there is a suggestion that the changes were less marked than in the sulfanilamide group.

Bone marrow.—The femoral bone marrow was examined in nine animals. It was essentially normal in six, moderately hypoplastic in two (the deficiency was chiefly in the granulocytes in rabbit 816 and in the normoblasts in rabbit 819), and slightly hyperplastic in rabbit

781, with an excess of immature granulocytes. Rabbit 750 showed slight nuclear fragmentation and degeneration, and rabbit 819 a small amount of brown pigment. As with the testis, the changes seemed slightly less in extent than with the sulfanilamide group.

Other organs.—The ovary of rabbit 829 and the gall bladder of rabbit 782 were negative.

SUMMARY

In the 15 rabbits given fatal doses of sulfanilyl sulfanilamide the histopathological changes were, for the most part, similar to those seen in the sulfanilamide-treated group, but were more pronounced and more frequent; this can best be seen in the following table (table 2). Exceptions to the rule were in the cases of voluntary muscle and, possibly, testis and bone marrow.

TABLE 2.—*Comparison of lesions in rabbits receiving sulfanilamide and sulfanilyl sulfanilamide*

Organ and lesion	Sulfanilamide		Sulfanilyl sulfanilamide	
	Number	Percent	Number	Percent
Lung:				
Pneumonitis	3 in 20	15	7 in 13	54
Liver:				
Fatty change	2 in 20	10	4 in 15	27
Spleen:				
Hemosiderosis ++ or greater	8 in 21	38	10 in 15	67
Active follicle reticulum	11 in 21	52	13 in 15	87
Kidney:				
Epithelial degeneration	3 in 20	15	6 in 15	40
Tubular casts	4 in 20	20	12 in 15	80
Dilated tubules	4 in 20	20	6 in 15	40
Sciatic nerve:				
Degenerative changes	3 in 15	20	8 in 13	62
Voluntary muscle:				
Degenerative changes	7 in 15	47	0 in 11	0

EFFECT OF SPECIAL DIETS

The rabbits' regular diet consisted of a mixture of oats and cabbage. Six of the rabbits which we examined had been on a diet of cabbage only and 12 on a diet of oats only, as indicated by "C" and "O," respectively, in table 1. Rosenthal (*1*) has noted fewer fatalities among rabbits on a diet of cabbage alone than among those on a diet of oats alone, when treated with sulfanilamide. Only one of our sulfanilamide rabbits had been on a cabbage diet. On the other hand, the rabbits treated with sulfanilyl sulfanilamide showed no difference in mortality rate when put on the different diets, and the pathological findings were essentially the same.

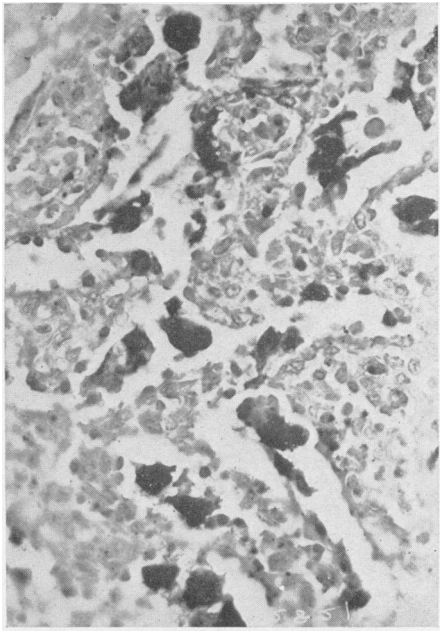

FIGURE 1.—Rabbit 786, sulfanilamide. Splenic hemosiderosis, grade + +. In this particular section the hemosiderin is chiefly in macrophages in the sinuses. ×365.

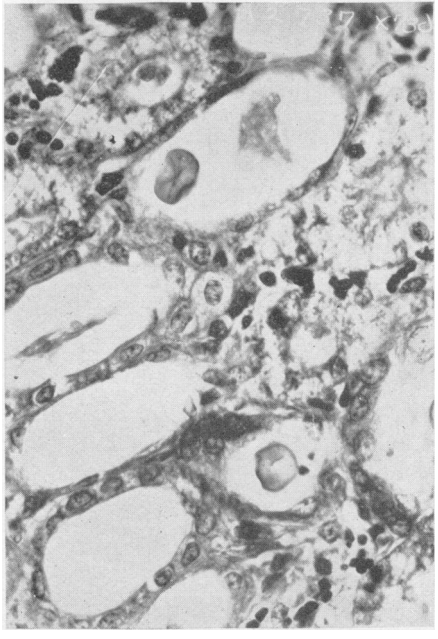

FIGURE 2.—Rabbit 752, sulfanilyl sulfanilamide. Doubly refractile radially striated crystalline bodies in renal tubules. ×365.

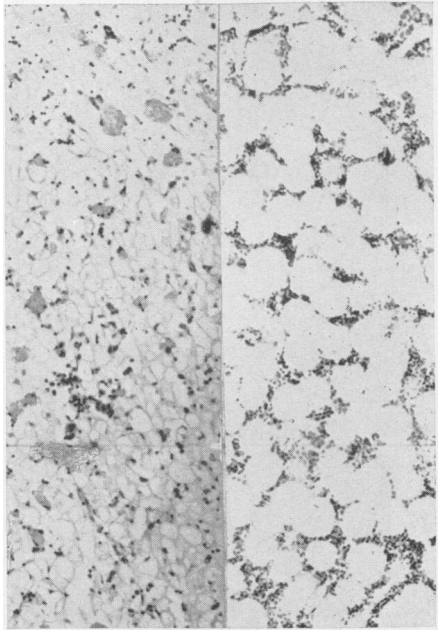

FIGURE 3.—Rabbit 819, sulfanilyl sulfanilamide. Moderately hypoplastic femoral bone marrow (left), compared with a normal rabbit bone marrow from the same location (right). ×92.

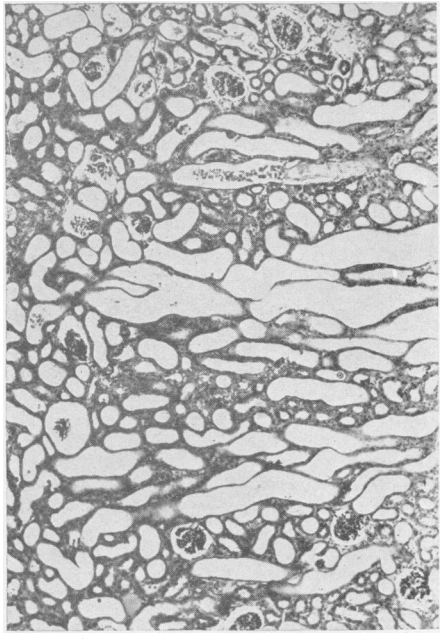

FIGURE 4.—Rabbit 749, sulfanilyl sulfanilamide. Marked dilatation of renal collecting tubules, with lesser degrees of dilatation of other tubules and of glomerular spaces. ×44.

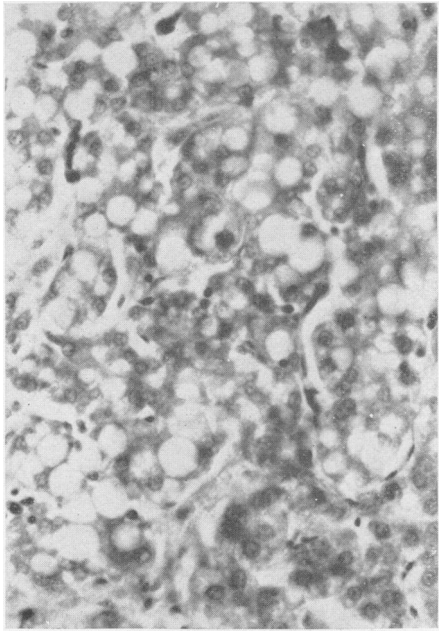

FIGURE 5.—Hen 761, sulfanilamide. Moderate fatty change of liver. ×365.

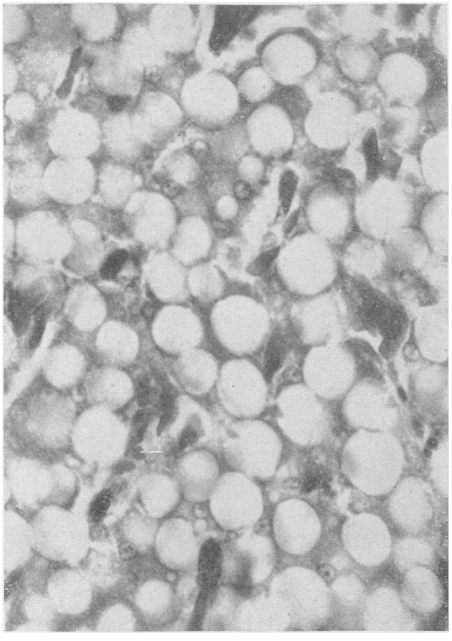

FIGURE 6.—Hen 787, sulfanilamide. Very marked fatty change of liver. ×470.

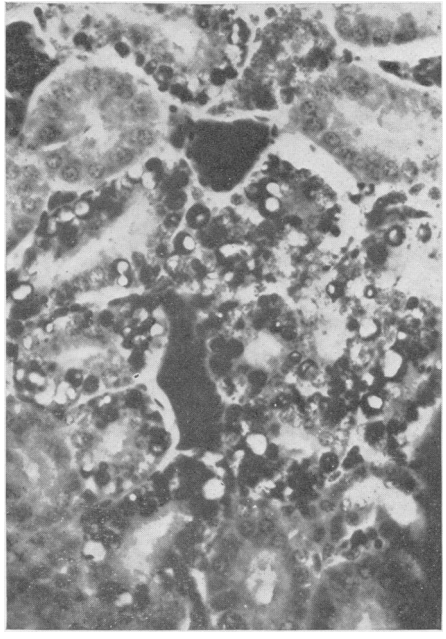

FIGURE 7.—Hen 761, sulfanilamide. Focal fatty change in epithelium of renal tubules. Scarlet red. ×365.

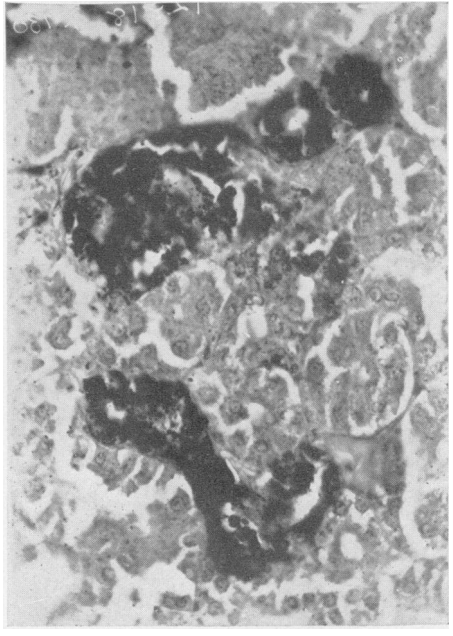

FIGURE 8.—Hen 761, sulfanilamide. Focal pigmentation of renal tubular epithelium. Perls' reaction for hemosiderin. ×365.

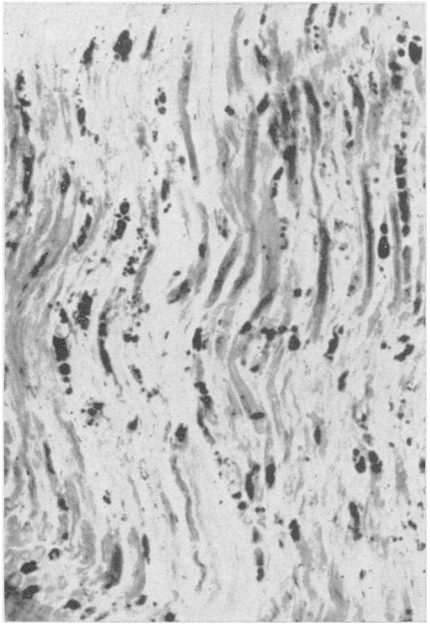

FIGURE 9.—Hen 102-911, sulfanilyl sulfanilamide. Rather marked myelin sheath degeneration in sciatic nerve. Marchi technique. ×75.

PATHOLOGICAL CHANGES IN 21 HENS TREATED WITH FATAL DOSES OF SULFANILAMIDE (TABLE 3)

CONTROL HENS

Because of the fact that not many hens have been examined histologically in this laboratory, 6 hens, supposedly normal, were used as control material and their tissues were examined in the same manner as that followed for the test animals; the findings are given in table 3.

EXPERIMENTAL ANIMALS

Lung.—The lung was examined in 20 animals and in general showed little change. In hen 668 a small number of polymorphonuclear leucocytes were scattered throughout the interalveolar septa, and in hen 796 a few bronchi contained amorphous oxyphilic debris and cells so necrotic that their nature could not be determined. Hen 759 showed moderate congestion. The remaining 17 lungs were negative.

Liver.—The liver was examined in all 21 animals; 17 showed a diffuse fatty change which was graded as slight in 1, moderate (fig. 5) in 6, marked in 5, and very marked (fig. 6) in 5. This was a distinct contrast with the control hens, in which none of the six livers showed fatty change; three of the controls were fat free with fat stains. Special examination for fat was made on 10 of the 21 livers; the detailed results may be seen in table 3. All but two livers contained brownish pigment granules in the Kupffer cells, while only two had pigment in the hepatic cells; in these two the amount of pigment in both the hepatic and Kupffer cells was large and Perls' reaction showed that the pigment was chiefly hemosiderin. Three other livers with pigment in the Kupffer cells were tested and in these the pigment was also chiefly hemosiderin. In general, the control livers had less pigment in the Kupffer cells, as will be seen from the table, and in these the pigment was also chiefly hemosiderin. The hepatic cells of one control hen (13543) also contained a small amount of hemosiderin.

Changes in the liver, apart from fatty change and the presence of hemosiderin, were not frequent, and in the control livers were absent. The liver of hen 798 showed moderate atrophy, and that of hen 841 slight focal coagulation necrosis. In hen 668 there were karyorrhectic leucocytes in the sinuses and portal spaces, and in hen 798 occasional hemocytoblasts in the sinuses. The liver of hen 763 showed damming of the bile in the small ducts, and that of hen 759 showed a marked increase in the number of paravenous lymphocytes.

Spleen.—The spleen was examined in 10 hens. In all of them hemosiderin was present, somewhat more in the pulp than in the sinuses; one was graded +, four were graded ++, and five, +++.

TABLE 3.—*Partial list of pathological changes found in hens after administration of fatal doses of sulfanilamide and sulfanilyl sulfanilamide*

Pharmacology No.	Pathology No.	Dosage: Grams per kilo daily	Dosage: Days given	Dosage: Total dose, grams	Day of death	Liver: Fatty change with usual stains	Liver: Sudanophilic material in hepatic cells	Liver: Anisotropic material in hepatic cells	Liver: Sudanophilic material in Kupffer cells	Liver: Anisotropic material in Kupffer cells	Liver: Hemosiderin in Kupffer cells	Hemosiderosis of spleen	Kidney: Tubular degenerative changes	Kidney: Casts and debris	Kidney: Doubly refractile concretions	Kidney: Pigment	Kidney: Fatty change	Peripheral neuritis	Lesions in heart	Lesions in voluntary muscle	Hypoplasia of bone marrow
SULFANILAMIDE																					
760	12788	1.4	1	1.4	3	++					++		0	0	0	0	0	++			
759	12805	0.9	1	0.9	11	+++					0		0	0	+++	+++	0	++	+	0	
761	12818	0.8	1	0.8	12	++	++	+			++		0	0	0	+++	++	++	0	S	
764	12819	(1)	9	4.5	14	++	++	0			+++		++	++	0	++	++	+	0	0	
794	12898	1.0	4	4.0	7	0					++	+++	0	0	0	0	0	0	0	0	
763	12902	(2)	9	3.5	31	++++					+++		++	0	0	0	0	++	+	0	
787	12955	0.8	3	2.4	25	++++					+++		0	0	0	++	+	±	+	0	
790	12969	1.1	4	4.5	21	+++					++		++	0	0	0	++	0	0		
799	12970	0.8	1	0.8	30	++					++		0	0	0	0	0	++		+++	0
789	13039	0.8	3	2.4	41	+++					++		0	0	0	0	0	++	0	0	+
798	13055	0.9	1	0.9	48	0					+++	+++	0	0	0	++	0	++		+++	0
796	13293	1.0	1	1.0	35	++++					+							±	0	S	++
797	13294	1.0	2	2.0	35	+++					+		0	0	0	+++	0	+	0	S	0
263-914	13645	1.0	9	9.0	42	++	++	0	+	0	+++	+++	0	+	0	0	+	±	+	0	+
848	13646	0.5	9	4.5	17	0	0	0	+++	+	+++	++	0	0	0	0	0	±	0	0	0
668	13647	0.7	9	6.3	17	0	0	0	+++	0	++	+++	+++	+	0	0	++	+	++	++	0
801	13660	1.0	9	9.0	24	++++	++++	+++			0	+	0	0	0	+++	+++	+	0		0
836	13661	0.5	9	4.5	20	++++	++++	+++			+++	++	0	0	0	++	++	±	0	0	++
841	13662	1.0	9	9.0	25	+	+	0	+	+	+++	++	0	0	0	0	0	±	0	0	+
837	13686	0.5	8	4.0	31	+++	+++	+			++++	+++	0	0	0	0	+	±	0	0	0
842	13687	1.0	9	9.0	34	++	++	0	(?)	+++	+++	++	0	0	0	0	0	+	0	0	
DISULFANILAMIDE																					
758	12793	0.9	6	5.4	25	++					+++		0	0	0	0	0	++		++	
102-911	13179	1.0	1	1.0	42	+					++	+	0	0	++	0	0	+++			0
586	13291	1.0	10	10.0	13	+++					++	+++	0	0	0	0	0	±	0	+	
622	13292	1.0	10	10.0	14	+++					+++	+++	0	0	0	++	0	±	0	0	

CONTROLS

795	13183	-------	-------	-------	-------	0	-------	-------	-------	-------	0	0	0	0	0	0	0	+	-------	0	0
865	13332	-------	-------	-------	-------	0	-------	-------	-------	-------	++	-------	0	+	0	0	0	++	-------	-------	-------
	13543	-------	-------	-------	-------	0	-------	-------	-------	-------	++	+	0	0	0	0	0	++	0	0	0
	14188	-------	-------	-------	-------	0	0	0	0	0	++	++	0	0	0	+	0	0	0	0	0
	14189	-------	-------	-------	-------	0	0	0	0	0	++	++	0	0	0	0	0	0	0	-------	0
	14190	-------	-------	-------	-------	0	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0

[1] 0.92 grams per kilo for 1 day, followed by 0.45 grams per kilo per day for 8 days.
[2] 0.7 grams per kilo for 1 day, followed by 0.35 grams per kilo per day for 8 days.
[3] S = Sarcosporidiosis.

Perls' reaction was done on four, and showed from two-thirds to nearly all of the pigment as hemosiderin. There was much less hemosiderin in the controls; of five spleens examined, one had practically none and four showed a + grade. In most of the spleens the periarterial reticular tissue was small to moderate in amount, and follicles could be made out only indistinctly; the control spleens were essentially similar. In the spleen of hen 798 the pulp macrophages contained in addition to the hemosiderin a few fragments of red cells; in this same spleen the pulp appeared hyperplastic, while in hen 848 it appeared hypoplastic. In hen 794 the periarterial reticular tissue was prominent and contained a moderate number of fragments of red cells. The control spleens showed nothing of note except the slight hemosiderosis.

Kidney.—The kidneys were examined in 20 of the 21 hens. They showed but little of the tubular degenerative changes, casts, etc., that the rabbit kidneys did; instead there were considerable amounts of fat (fig. 7) and pigment (fig. 8) in the epithelium of the convoluted, Henle loop, and collecting tubules, in that order of frequency. Nine of the twenty kidneys contained fat in small to large amounts, and 8 contained brown pigment (50 to 75 percent hemosiderin) in moderate to large amounts. Fat stains were done on eight of the nine kidneys which showed fatty change, and two others; no anisotropic material was seen in any of these. The pigment and fat had about the same tubular distribution; usually the pigment foci were somewhat separated from the fatty foci, but they sometimes overlapped each other, and cells could not infrequently be seen containing both fat and pigment. In the control hens, only one of the six kidneys contained pigment (grade +) and none showed fat; fat stains were done on four of the six and all were fat free; Perls' reaction on two of the five showing no pigment was negative.

Inter- and peri-tubular lymphocyte infiltration was noted in 5 of the 20; it was slight in degree except for hen 763, in which it was moderate. Whether this had any relation to the sulfanilamide treatment is difficult to say; it was not seen in the controls. The kidney of hen 759 contained numerous doubly refractile masses similar to those seen in the rabbit kidneys, and hen 763 showed a moderate tubular dilatation. Tubular degenerative changes (hyalinization, necrosis, vacuolation, karyopyknosis, etc.), chiefly in the convoluted tubules and to a lesser extent in the Henle loops, were seen in moderate degree in three kidneys and markedly in one; small to large amounts of casts and debris were seen in the tubules of three kidneys. None of these changes were seen in the controls except in hen 865, where the tubules contained a small number of hyaline casts. This same kidney showed a peculiar lesion not seen in any other of our animals; some of the largest collecting tubules were dilated and filled with colorless sheets

and irregular masses of doubly refractile (in paraffin section) material together with foreign body giant cells. We have no explanation for this lesion.

Brain and spinal cord.—The brain was examined in 11 hens and was negative in all. Sections usually included temporal and parietal cortex, thalamus, optic lobes, midbrain, cerebellum, and medulla.

From one to three sections of the spinal cord were examined in nine hens; all except two were negative. In hen 760 a section of cervical cord stained by the Marchi method showed a few peripheral fibers in the midlateral and anteromedial regions with ballooning of the fibers and blackening of the myelin; in hen 798 occasional lumbar anterior horn cells showed moderate numbers of vacuoles containing spherical eosinophilic bodies; the nuclei appeared normal, and sections of the cervical and thoracic levels were negative. Sections of cord were made in five of the controls and were negative.

Peripheral nerves.—The sciatic nerve was examined in all 21 animals. Seven animals showed a moderate degree of degenerative changes (swelling and rarefaction of segments of nerve fibers, fragmentation of axis cylinders, and blackening of fragmented myelin with osmic acid), five a slight degree, eight a minimal degree, and one, none. Of the six control animals, two showed slight changes, one, minimal, and three, none. We graded the nerves as showing minimal or $\pm$ changes when only a few small scattered degenerated segments were seen, slight or $+$ when about 1 percent of the total mass of the myelin was degenerated, moderate or $++$ with about 5 percent and $+++$ with 10 to 15 percent degenerated; the latter grade was seen in only one animal (hen 102–911, sulfanilyl sulfanilamide) and is illustrated in figure 9. These percentages may seem small, but it must be remembered that the blackened degenerated myelin (with the Marchi method) stands out conspicuously, and a small amount gives an appearance of much degeneration. We cannot explain the degeneration seen in the nerves of the control hens. The grade $++$ degeneration seen in seven of the sulfanilamide group was considerably greater in amount, and is probably a result of the treatment. None of the hens, treated or control, showed any evidence of neurolymphomatosis gallinarum (*11*, *12*), a common fowl disease in which there are lymphoid infiltrations in the peripheral nerves, together with a clinical paralysis.

Gastrointestinal tract.—The gastrointestinal tract was examined in 16 hens; 2 or 3 different portions from each hen were usually sectioned; the total number of sections was 42, divided as follows: esophagus 3, crop 5, proventriculus 7, gizzard 10, small intestine 11, cecum 4, colon 1, and cloaca 1. No significant changes were seen. In three hens (799, 848, and 668) there were parasitic worms in the esophagus, crop, and gizzard, respectively; in two (263–914 and 668)

there was a suppurative inflammation in the tip of the cecum, a lesion probably unconnected with the experiment. Four hens (798, 841, 837, and 842) showed small to moderate numbers of small clumps of macrophages in the serosa; the macrophages contained greenish-brown pigment, presumably hemosiderin (in two of the four Perls' reaction was done, with nearly all pigment becoming blue); two of five control hens in which sections of gut were examined showed similar pigment, partly iron-containing.

Heart.—Examined in 17 animals; 12 of these were negative, and two of these stained for fat were fat free. Of the five others, hen 759 showed moderate focal subacute pericarditis, hen 763 a 0.4-mm peripheral focus of recent myocardial scarring, hen 787 a slight diffuse myocardial atrophy, and hen 263–914 occasional small myocardial foci of lymphocytes and polymorphonuclears, with some atrophy of the muscle fibers. Hen 668 showed a moderate focal epicardial and myocardial infiltration with lymphocytes and some polymorphonuclears; the process was more acute in the epicardium, where the exudate was about one-half polymorphonuclear and there were a few areas of serosal cell and fibroblast proliferation. The heart was examined in four control hens and all were negative and fat free.

Voluntary muscle.—Voluntary muscle from the thigh was examined in 18 animals; 12 of these were negative. Three muscles contained Sarcosporidia, without other lesions. In hen 799 there was marked hydropic change; hen 798 showed marked focal atrophy and coagulation necrosis. The muscle of hen 668 showed some atrophy and the fibers contained numerous small vacuoles; osmic acid stain was negative; there were a few lymphocyte and polymorphonuclear infiltrations, chiefly perivascular. The muscle in four control hens was negative.

Pancreas.—The pancreas of hen 837 showed a few small scattered lymphocytic foci; in the three other treated animals and in the five controls in which it was examined it was negative.

Adrenal.—The adrenal was examined in hens 763 and 787 and appeared normal.

Ovary and oviduct.—No lesions were seen in the nine ovaries examined. The oviduct of hen 794 was negative; in hen 797 the lumen contained two calcified laminated structures, the largest 0.2 mm in diameter. Five of the six control ovaries showed no lesions; in hen 865 the ovary contained a 1 cm follicle which showed, inside its granulosa cell layer, nuclear debris and bacteria; this same animal also had inside its abdomen a 5 by 9 cm mass of hard yolk-like amorphous material, focally showing numerous necrotic polymorphonuclears and masses of bacteria.

Bone marrow.—The femoral bone marrow was examined in 12 animals; five were essentially normal when compared with the marrow of five control hens (one to eight different bones from each control hen, with a total of 15 bones). Five of the remaining seven showed slight or moderate degrees of hypoplasia; in some the marrow was grossly fatty instead of red. In hens 798 and 848 lymphocytes appeared slightly increased in numbers; the granulocytes were slightly if at all reduced. Hen 837 showed from two-thirds to three-fourths of the marrow cavity filled with irregular new bone, but the marrow present was normal. As in the rabbit, the femoral marrow of the hen is less cellular in the center than at the periphery of the bone in the transverse plane, and care was taken to examine cross-sections as well as longitudinal sections of the femur. In the rabbit the femoral marrow shells out easily as a smooth cylinder after cracking the bone, but in the hen the spongy bone intermingles with the marrow to a variable extent and it is necessary to section bone as well as marrow properly to study the latter.

The hypoplasia affected chiefly the granulocytes, and in some instances they were markedly reduced in number; red cell formation (intrasinusoidal) was little affected. With decrease in the number of granulocytes there was often an increase, actual as well as relative, in the number of lymphocytes.

SUMMARY

The pathological changes produced by fatal doses of sulfanilamide in a group of 21 hens were generally marked. The most severe lesion was fatty change of the liver; other lesions were bone marrow hypoplasia, deposition of fat and hemosiderin in the kidneys, slight peripheral neuritis, degenerative renal tubular changes, splenic and hepatic (chiefly Kupffer cell) hemosiderosis, and occasional lesions in the heart and voluntary muscles.

One point to be remembered is that the hens survived longer after the beginning of drug administration (25 days average) than did the rabbits, giving greater opportunity for the development of microscopically visible pathological changes. On the other hand, the group of rabbits treated with sulfanilyl sulfanilamide showed greater changes than the group treated with sulfanilamide, even though the average period of survival was less (7.7 versus 11.2 days).

SULFANILYL SULFANILAMIDE IN HENS

Four hens had been given sulfanilyl sulfanilamide. With such a small number no conclusions can be drawn; in general the changes were similar to those produced by sulfanilamide (see table 3).

OTHER ANIMALS

At the beginning of this study the tissues of a group of 4 rats which had been given 0.5 grams per kilo of sulfanilyl sulfanilamide daily by mouth for one month were studied microscopically; no lesions, or only minor ones, were seen in the liver, spleen, lung, kidney, thymus, stomach, and heart.

SUMMARY

The histopathological changes in 61 hens and rabbits receiving fatal doses of sulfanilamide and sulfanilyl sulfanilamide (usually at the rate of 0.5 to 1 gram per kilo per day) have been studied in detail.

The hens usually showed quite marked histopathological changes, with a fatty liver as the chief lesion, together with fat and hemosiderin deposition in the kidney, hemosiderin in the spleen and Kupffer cells, and frequently peripheral neuritis and hypoplasia of the bone marrow.

The rabbits treated with sulfanilyl sulfanilamide usually showed changes of moderate degree, chiefly renal degenerative changes, splenic hemosiderosis, slight peripheral neuritis, focal pneumonitis, hypo- or hyperplasia of the bone marrow, degenerative testicular changes, and peculiar doubly refractile concretions in the kidneys.

The rabbits treated with sulfanilamide showed about the same type of changes as those treated with sulfanilyl sulfanilamide, but they were usually less marked and less frequently present; one exception was the presence of degenerative changes in voluntary muscle.

Central nervous system lesions which might be attributed to the experimental procedures were rare in all groups of animals.

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DEATHS DURING WEEK ENDED JANUARY 7, 1939

[From the Weekly Health Index, issued by the Bureau of the Census, Department of Commerce]

	Week ended Jan. 7, 1939	Corresponding week, 1938
Data from 88 large cities of the United States:		
Total deaths	9,145	[1] 9,515
Average for 3 prior years	10,350	----------
Deaths under 1 year of age	569	[1] 551
Average for 3 prior years	[1] 629	----------
Data from industrial insurance companies:		
Policies in force	68,314,978	69,937,677
Number of death claims	9,375	11,288
Death claims per 1,000 policies in force, annual rate	7.2	8.4

[1] Data for 86 cities.

PREVALENCE OF DISEASE

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

CURRENT WEEKLY STATE REPORTS

These reports are preliminary, and the figures are subject to change when later returns are received by the State health officers.

In these and the following tables, a zero (0) indicates a positive report and has the same significance as any other figure, while leaders (----) represent no report, with the implication that cases or deaths may have occurred but were not reported to the State health officer.

Cases of certain diseases reported by telegraph by State health officers for the week ended January 14, 1939, rates per 100,000 population (annual basis), and comparison with corresponding week of 1938 and 5-year median

Division and State	Diphtheria				Influenza				Measles			
	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median
NEW ENG.												
Maine	79	13	3	2	18	3	7	7	206	34	66	66
New Hampshire	0	0	0	0	----	----	----	----	10	1	39	39
Vermont	0	0	0	0	----	----	----	----	147	11	248	33
Massachusetts	4	3	4	12	----	----	----	----	519	441	95	287
Rhode Island	8	1	0	0	----	----	----	----	38	5	1	13
Connecticut	6	2	7	5	18	6	10	12	547	184	17	87
MID. ATL.												
New York	15	37	31	54	[1] 39	[1] 57	[1] 14	[1] 17	536	1,338	389	652
New Jersey	16	13	18	18	29	24	13	26	26	22	824	110
Pennsylvania	17	33	64	73	----	----	----	----	55	109	5,474	946
E. NO. CEN.												
Ohio	25	33	34	55	----	----	----	100	18	24	1,094	239
Indiana	30	20	65	51	16	11	11	75	13	9	277	170
Illinois	43	65	37	45	8	12	28	57	32	48	1,978	147
Michigan [2]	7	7	13	13	----	----	2	7	466	440	579	82
Wisconsin	2	1	4	6	114	65	34	35	829	471	501	157
W. NO. CEN.												
Minnesota	4	2	4	7	4	2	2	1	1,947	1,003	9	97
Iowa	12	6	4	12	8	4	5	15	327	161	34	34
Missouri	37	29	21	37	76	59	118	215	5	4	1,251	193
North Dakota	0	0	0	0	81	11	2	5	1,824	249	5	27
South Dakota	75	10	1	1	----	----	1	1	3,368	447	----	26
Nebraska	11	3	4	4	----	----	----	----	164	43	2	17
Kansas	20	7	14	14	25	9	32	32	34	12	158	29
SO. ATL.												
Delaware	39	2	2	2	----	----	2	3	----	----	2	12
Maryland [2 3 4]	19	6	8	14	15	5	15	26	1,451	470	11	98
District of Columbia	81	10	5	13	16	2	1	5	89	11	7	9
Virginia [3]	96	51	21	32	789	420	----	----	315	168	212	212
West Virginia	38	14	16	16	35	13	52	72	145	54	261	17
North Carolina [4]	48	33	25	30	10	7	26	49	635	434	627	627
South Carolina [4]	27	10	2	5	1,355	495	673	673	19	7	134	62
Georgia [4]	27	16	10	10	226	136	----	----	120	72	185	----
Florida	36	12	25	9	3	1	11	11	136	45	65	11

See footnotes at end of table.

Cases of certain diseases reported by telegraph by State health officers for the week ended January 14, 1939, rates per 100,000 population (annual basis), and comparison with corresponding week of 1938 and 5-year median—Continued

Division and State	Diphtheria				Influenza				Measles			
	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median
E. SO. CEN.												
Kentucky	31	18	15	20	113	65	61	79	12	7	157	84
Tennessee	21	12	19	26	113	64	252	252	118	67	250	42
Alabama [4]	11	6	19	20	337	191	300	352	222	126	157	137
Mississippi [3]	20	8	4	9	------	------	------	------	------	------	------	------
W. SO. CEN.												
Arkansas	27	11	25	16	504	203	182	161	52	21	236	26
Louisiana [4]	53	22	22	21	87	36	51	16	148	61	2	23
Oklahoma	28	14	22	17	300	149	100	120	119	59	15	15
Texas [4]	40	48	68	74	594	716	619	619	179	216	84	84
MOUNTAIN												
Montana	9	1	0	1	244	26	------	7	3,871	412	1	4
Idaho	10	1	2	2	20	2	6	4	471	46	10	24
Wyoming	22	1	3	0	------	------	------	------	175	8	1	4
Colorado	87	18	12	7	101	21	------	------	135	28	108	11
New Mexico	25	2	3	4	12	1	2	9	358	29	147	41
Arizona	98	8	6	2	1,439	117	51	67	37	3	------	8
Utah [3]	0	0	5	1	10	1	------	------	268	27	72	72
PACIFIC												
Washington	3	1	0	3	12	4	1	1	436	141	25	58
Oregon	5	1	7	2	194	39	35	35	134	27	8	27
California [4]	34	41	33	33	34	41	86	86	1,858	2,262	116	144
Total	26	652	707	816	142	3,018	2,805	2,805	399	9,857	15,934	12,529
2 weeks	26	1,291	1,401	1,516	148	6,273	5,228	5,228	334	16,527	29,082	21,107

Division and State	Meningitis, meningococcus				Poliomyelitis				Scarlet fever			
	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38 median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38 median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38 median
NEW ENG.												
Maine	0	0	1	0	0	0	0	0	60	10	16	16
New Hampshire	0	0	0	0	0	0	0	0	81	8	18	18
Vermont	0	0	0	0	0	0	0	0	80	6	8	12
Massachusetts	1.2	1	1	2	0	0	0	0	225	191	344	260
Rhode Island	0	0	0	0	0	0	0	0	23	3	32	26
Connecticut	0	0	1	0	0	0	1	0	217	73	86	77
MID. ATL.												
New York	4	10	4	5	0	0	1	1	193	481	564	687
New Jersey	0	0	4	3	0	0	0	0	216	181	111	158
Pennsylvania	1	2	6	4	0	0	0	1	179	352	630	630
E. NO. CEN.												
Ohio	0.8	1	6	6	0.8	1	2	2	385	500	544	544
Indiana	0	0	3	3	0	0	0	0	420	282	157	174
Illinois	0	0	7	10	0.7	1	1	0	360	548	707	707
Michigan [3]	0	0	2	2	0	0	1	0	542	512	500	346
Wisconsin	1.8	1	0	2	1.8	1	1	0	535	304	203	288

See footnotes at end of table.

Cases of certain diseases reported by telegraph by State health officers for the week ended January 14, 1939, rates per 100,000 population (annual basis), and comparison with corresponding week of 1938 and 5-year median—Continued

Division and State	Meningitis, meningococcus				Poliomyelitis				Scarlet fever			
	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38 median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38 median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38 median
W. NO. CEN.												
Minnesota	2	1	0	1	0	0	0	0	264	136	134	147
Iowa	2	1	0	1	0	0	0	0	217	107	246	156
Missouri	1.3	1	0	1	0	0	0	0	191	148	286	193
North Dakota	0	0	0	0	0	0	0	0	154	21	39	39
South Dakota	0	0	0	0	8	1	0	0	166	22	26	26
Nebraska	0	0	0	0	0	0	0	0	115	30	44	67
Kansas	0	0	2	2	2.8	1	0	0	448	160	199	143
SO. ATL.												
Delaware	20	1	0	0	0	0	0	0	0	0	19	13
Maryland [2 3 4]	0	0	0	3	0	0	0	0	204	66	49	100
Dist. of Col	0	0	1	1	0	0	0	0	97	12	26	24
Virginia [3]	6	3	3	4	0	0	0	0	111	59	27	66
West Virginia	2.7	1	4	4	0	0	0	0	242	90	87	67
North Carolina [4]	2.9	2	4	3	1.5	1	0	0	92	63	49	63
South Carolina [4]	2.7	1	3	0	0	0	0	1	33	12	7	9
Georgia [4]	0	0	0	1	0	0	0	0	48	29	23	18
Florida	0	0	5	2	3	1	1	0	24	8	12	8
E. SO. CEN.												
Kentucky	3	2	6	6	0	0	1	0	214	123	61	66
Tennessee	5	3	7	5	0	0	1	0	85	48	35	50
Alabama [4]	9	5	18	4	1.8	1	1	0	42	24	15	24
Mississippi [3]	2.5	1	2	1	2.5	1	0	0	23	9	9	13
W. SO. CEN.												
Arkansas	0	0	0	0	0	0	2	0	45	18	23	13
Louisiana [4]	5	2	1	1	0	0	1	1	36	15	28	28
Oklahoma	0	0	0	2	0	0	0	0	95	47	50	36
Texas [4]	1.7	2	1	4	1.7	2	1	1	92	111	165	125
MOUNTAIN												
Montana	0	0	1	1	0	0	0	0	225	24	56	56
Idaho	0	0	1	0	0	0	0	0	92	9	29	19
Wyoming	0	0	0	0	0	0	0	0	175	8	10	14
Colorado	5	1	0	1	0	0	0	0	241	50	61	61
New Mexico	0	0	1	1	0	0	0	0	173	14	24	25
Arizona	0	0	0	1	0	0	0	0	86	7	11	22
Utah [3]	10	1	3	0	0	0	0	0	328	33	75	26
PACIFIC												
Washington	0	0	1	0	3	1	0	1	188	61	56	48
Oregon	0	0	0	0	5	1	0	0	329	66	67	63
California [4]	0.8	1	7	3	2.5	3	2	7	169	206	218	323
Total	1.8	44	106	106	0.6	16	17	26	211	5,287	6,186	6,270
2 weeks	2.1	104	201	201	0.6	32	37	47	194	9,746	11,210	11,437

Division and State	Smallpox				Typhoid and paratyphoid fever				Whooping cough		
	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 14, 1938, cases
NEW ENG.											
Maine	0	0	0	0	0	0	1	1	254	42	57
New Hampshire	0	0	0	0	0	0	0	0	10	1	3
Vermont	0	0	0	0	0	0	0	0	1,247	93	24
Massachusetts	0	0	0	0	4	3	2	2	267	227	154
Rhode Island	0	0	0	0	0	0	0	0	658	86	33
Connecticut	0	0	0	0	3	1	0	0	336	113	39

See footnotes at end of table.

Cases of certain diseases reported by telegraph by State health officers for the week ended January 14, 1939, rates per 100,000 population (annual basis), and comparison with corresponding week of 1938 and 5-year median—Continued

Division and State	Smallpox				Typhoid and paratyphoid fever				Whooping cough		
	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 15, 1938, cases	1934–38, median	Jan. 14, 1939, rate	Jan. 14, 1939, cases	Jan. 14, 1938, cases
MID. ATL.											
New York	0	0	0	0	3	8	3	7	303	755	330
New Jersey	0	0	0	0	5	4	1	4	618	518	150
Pennsylvania	0	0	0	0	8	16	13	13	236	464	362
E. NO. CEN.											
Ohio	46	60	9	2	4	5	3	3	200	260	144
Indiana	144	97	66	5	1	1	2	0	37	25	36
Illinois	7	10	79	14	1	1	5	5	307	467	100
Michigan [2]	2	2	4	1	2	2	3	3	233	220	184
Wisconsin	11	6	5	13	0	0	0	0	560	318	182
W. NO. CEN.											
Minnesota	83	43	95	7	4	2	1	1	74	38	55
Iowa	26	13	78	12	0	0	0	0	24	12	32
Missouri	24	19	50	5	8	6	34	3	26	20	95
North Dakota	15	2	12	12	0	0	0	0	22	3	14
South Dakota	38	5	2	14	8	1	0	0	8	1	6
Nebraska	27	7	1	3	4	1	3	0	19	5	6
Kansas	101	36	23	13	3	1	5	3	25	9	93
SO. ATL.											
Delaware	0	0	0	0	0	0	0	0	118	6	7
Maryland [2 3 4]	0	0	0	0	0	0	2	4	127	41	45
Dist. of Col.	0	0	0	0	0	0	1	1	227	28	9
Virginia [2]	0	0	0	0	2	1	2	5	106	53	108
West Virginia	0	0	0	0	35	13	2	2	97	36	108
North Carolina [4]	0	0	0	0	1	1	4	4	416	284	324
South Carolina [4]	0	0	0	0	3	1	1	1	200	73	49
Georgia [4]	13	8	0	0	3	2	2	3	23	14	20
Florida	3	1	0	0	6	2	3	1	42	14	10
E. SO. CEN.											
Kentucky	5	3	34	1	12	7	0	7	16	9	14
Tennessee	2	1	2	0	4	2	7	5	37	21	26
Alabama [4]	0	0	0	0	9	5	1	2	49	28	29
Mississippi [2]	0	0	24	0	8	3	1	1			
W. SO. CEN.											
Arkansas	22	9	10	2	5	2	0	3	22	9	48
Louisiana [4]	2	1	0	1	19	8	4	9	2	1	6
Oklahoma	22	11	2	1	8	4	1	2	2	1	12
Texas [4]	18	22	21	6	3	4	14	21	80	96	181
MOUNTAIN											
Montana	19	2	9	9	19	2	0	0	244	26	32
Idaho	143	14	58	2	0	0	1	1	20	2	11
Wyoming	44	2	2	2	0	0	0	0	131	6	10
Colorado	130	27	15	4	10	2	0	0	212	44	5
New Mexico	0	0	7	0	62	5	1	4	259	21	60
Arizona	184	15	0	0	12	1	0	0	74	6	37
Utah [2]	10	1	0	0	0	0	0	0	119	12	59
PACIFIC											
Washington	25	8	38	31	0	0	4	2	74	24	115
Oregon	70	14	20	8	15	3	3	0	120	24	13
California [4]	14	17	71	10	2	2	0	5	85	103	456
Total	18	456	737	253	5	122	130	139	189	4,659	3,893
2 weeks	15	747	1,196	416	4	220	253	276	169	8,354	7,520

[1] New York City only.
[2] Period ended earlier than Saturday.
[3] Rocky Mountain spotted fever, week ended Jan. 14, 1939, 2 cases as follows: Maryland, 1; Virginia, 1.
[4] Typhus fever, week ended Jan. 14, 1939, 51 cases as follows: Maryland, 1; North Carolina, 1; South Carolina, 5; Georgia, 24; Alabama, 11; Louisiana, 2; Texas, 6; California, 1.

SUMMARY OF MONTHLY REPORTS FROM STATES

The following summary of cases reported monthly by States is published weekly and covers only those States from which reports are received during the current week:

State	Meningitis, meningococcus	Diphtheria	Influenza	Malaria	Measles	Pellagra	Poliomyelitis	Scarlet fever	Smallpox	Typhoid and paratyphoid fever
November 1938										
Florida		40	7	61	92	20		48	0	6
Montana	2	7	30		702		1	124	13	19
December 1938										
District of Columbia	0	42	19		6			32	0	1
Florida	6	35	18	45	61	15	1	46	0	13
Georgia	1	63	441	59	215	25	7	102	2	31
North Carolina	4	251	16	29	1,183	25	2	267	0	6
Texas	9	260	1,800	208		73	5	495		91
Vermont	0	0			12		0	29	0	0
West Virginia	10	85	85		98		0	294	0	10
Wyoming	0	24			45		0	28	8	2

November 1938

Florida:	Cases
Anthrax	1
Chickenpox	21
Dysentery (amoebic)	6
Hookworm disease	288
Mumps	11
Rabies in animals	3
Rabies in man	1
Septic sore throat	5
Tetanus	3
Typhus fever	5
Undulant fever	5
Vincent's infection	23
Whooping cough	38
Montana:	
Chickenpox	345
Dysentery (bacillary)	1
German measles	5
Impetigo contagiosa	18
Mumps	7
Scabies	6
Septic sore throat	7
Whooping cough	167

December 1938

Chickenpox:	
District of Columbia	32
Florida	70
Georgia	187
North Carolina	307
Vermont	331
West Virginia	238
Wyoming	34
Conjunctivitis, infectious:	
Georgia	1

December 1938—Con.

Dengue:	Cases
Florida	1
Dysentery:	
Florida (amoebic)	3
Georgia (amoebic)	13
Georgia (bacillary)	8
Encephalitis, epidemic or lethargic:	
District of Columbia	1
Texas	3
German measles:	
North Carolina	17
Vermont	6
Wyoming	5
Hookworm disease:	
Florida	392
Georgia	1,569
Mumps:	
Florida	29
Georgia	65
Vermont	69
West Virginia	26
Wyoming	73
Puerperal septicemia:	
Georgia	1
Rabies in man:	
West Virginia	1
Rocky Mountain spotted fever:	
District of Columbia	1
North Carolina	1
Septic sore throat:	
Florida	2
Georgia	34
North Carolina	13

December 1938—Con.

Septic sore throat—Con.	Cases
West Virginia	1
Wyoming	3
Tetanus:	
Georgia	3
Trachoma:	
Georgia	1
Tularaemia:	
District of Columbia	4
Georgia	5
North Carolina	11
West Virginia	20
Typhus fever:	
Florida	12
Georgia	75
North Carolina	11
Undulant fever:	
District of Columbia	1
Florida	1
Georgia	7
North Carolina	2
Vermont	2
West Virginia	2
Wyoming	1
Vincent's infection:	
Florida	24
North Carolina	4
Vermont	10
Whooping cough:	
District of Columbia	82
Florida	78
Georgia	57
North Carolina	933
Vermont	297
West Virginia	115
Wyoming	9

WEEKLY REPORTS FROM CITIES

City reports for week ended January 7, 1939

This table summarizes the reports received weekly from a selected list of 140 cities for the purpose of showing a cross section of the current urban incidence of the communicable diseases listed in the table.

State and city	Diphtheria cases	Influenza		Measles cases	Pneumonia deaths	Scarlet fever cases	Smallpox cases	Tuberculosis deaths	Typhoid fever cases	Whooping cough cases	Deaths, all causes
		Cases	Deaths								
Data for 90 cities:											
5-year average	210	899	132	2,051	1,010	1,593	26	374	24	1,647	----
Current week [1]	145	208	74	1,954	811	1,229	45	332	21	1,411	----
Maine:											
Portland	1	----	0	0	1	0	0	0	0	9	32
New Hampshire:											
Concord	0	----	0	0	1	1	0	0	0	0	7
Manchester	0	----	0	0	3	3	0	0	0	0	17
Nashua	0	----	0	0	0	1	0	1	0	0	5
Vermont:											
Barre	0	----	0	0	0	1	0	1	0	12	5
Burlington	0	----	0	0	0	0	0	0	0	9	10
Rutland	0	----	0	0	1	0	0	0	0	0	8
Massachusetts:											
Boston	1	----	0	110	17	58	0	13	0	41	232
Fall River	0	----	1	0	0	0	0	1	0	0	20
Springfield	0	----	0	31	1	0	0	0	0	4	29
Worcester	1	----	0	1	4	6	0	3	0	20	40
Rhode Island:											
Pawtucket	0	----	0	0	1	3	0	0	0	0	20
Providence	0	----	1	1	5	2	0	3	0	39	73
Connecticut:											
Bridgeport	0	2	0	0	1	4	0	0	0	1	24
Hartford	1	5	0	30	4	0	0	1	0	6	40
New Haven	0	----	0	3	3	2	0	2	0	6	37
New York:											
Buffalo	0	----	0	35	10	31	0	9	0	38	144
New York	22	44	5	74	132	118	0	64	2	204	1,644
Rochester	0	----	0	30	4	7	0	1	0	12	75
Syracuse	0	----	0	2	7	10	0	0	0	9	52
New Jersey:											
Camden	0	1	1	1	3	7	0	1	1	2	31
Newark	0	4	0	2	11	37	0	6	1	54	104
Trenton	1	----	1	0	1	5	0	1	0	4	40
Pennsylvania:											
Philadelphia	7	8	4	13	37	51	0	23	0	111	510
Pittsburgh	6	3	4	4	24	37	0	12	1	32	204
Reading	0	----	0	2	0	1	0	1	0	1	21
Scranton	0	----	----	0	----	16	0	----	0	8	----
Ohio:											
Cincinnati	2	----	1	1	14	17	0	5	0	3	146
Cleveland	2	7	1	5	27	53	0	7	0	66	222
Columbus	2	2	2	1	6	7	0	4	0	3	117
Toledo	1	----	0	2	7	15	0	2	0	17	78
Indiana:											
Anderson	0	----	0	0	2	2	0	0	0	0	10
Fort Wayne	4	----	0	1	3	7	0	1	0	0	27
Indianapolis	6	----	4	2	20	55	33	1	0	11	106
Muncie	0	----	0	0	2	1	0	1	0	0	12
South Bend	0	----	0	0	1	6	0	0	0	0	21
Terre Haute	----	----	----	----	----	----	----	----	----	----	----
Illinois:											
Alton	0	----	0	0	1	1	0	0	0	0	14
Chicago	16	8	5	17	71	164	0	35	0	293	807
Elgin	0	----	0	0	4	3	0	0	0	0	16
Moline	0	----	0	0	0	0	0	0	0	0	6
Springfield	0	----	0	0	3	4	0	0	0	2	34
Michigan:											
Detroit	2	----	0	8	26	123	0	13	1	118	293
Flint	0	----	0	201	11	27	0	0	0	1	33
Grand Rapids	0	----	0	4	2	14	0	1	0	0	40
Wisconsin:											
Kenosha	0	----	0	0	1	4	0	0	0	14	15
Madison	0	----	0	2	2	5	0	0	0	10	17
Milwaukee	0	1	1	4	8	64	0	1	0	91	118
Racine	0	----	0	0	0	5	0	0	0	2	12
Superior	0	----	0	0	1	1	0	0	0	0	8

[1] Figures for Terre Haute, Ind., and Fargo, N. Dak., estimated; reports not received.

City reports for week ended January 7, 1939—Continued

State and city	Diphtheria cases	Influenza		Measles cases	Pneumonia deaths	Scarlet fever cases	Smallpox cases	Tuberculosis deaths	Typhoid fever cases	Whooping cough cases	Deaths, all causes
		Cases	Deaths								
Minnesota:											
Duluth	0	------	0	0	3	1	0	2	0	12	22
Minneapolis	0	------	1	68	9	21	0	0	0	12	129
St. Paul	0	------	0	346	8	20	0	0	0	5	73
Iowa:											
Cedar Rapids	0	------	-------	0	-------	1	0	-------	0	0	-------
Davenport	0	------	-------	0	-------	5	3	-------	0	0	-------
Des Moines	0	------	0	0	0	8	0	0	0.	0	31
Sioux City	0	------	0	65	-------	7	0	-------	0	3	-------
Waterloo	2	------	-------	1	-------	6	0	-------	0	3	-------
Missouri:											
Kansas City	0	------	1	0	9	30	0	4	0	1	93
St. Joseph	0	------	0	0	4	0	0	1	0	1	16
St. Louis	4	------	1	0	23	30	3	10	1	8	247
North Dakota:											
Fargo	-------	------	-------	-------	-------	-------	-------	-------	-------	-------	-------
Grand Forks	1	------	-------	0	-------	1	0	-------	0	0	-------
Minot	0	------	0	49	0	0	0	0	0	0	10
South Dakota:											
Aberdeen	0	------	-------	0	-------	1	1	0	-------	0	-------
Sioux Falls	0	------	0	248	0	0	0	0	0	0	7
Nebraska:											
Lincoln	0	------	-------	3	-------	1	0	-------	0	0	-------
Omaha	0	------	1	6	9	11	0	0	0	0	53
Kansas:											
Lawrence	0	2	0	0	1	0	0	0	0	0	5
Topoka	0	------	0	0	2	3	0	0	0	2	9
Wichita	0	------	0	0	4	4	0	1	0	0	23
Delaware:											
Wilmington	1	------	0	1	4	2	0	1	1	0	44
Maryland:											
Baltimore	0	3	1	226	27	12	0	11	0	21	247
Cumberland	0	------	0	0	1	0	0	0	0	0	12
Frederick	0	------	0	0	0	0	0	0	0	0	6
District of Col.:											
Washington	7	3	1	3	7	11	0	9	0	21	173
Virginia:											
Lynchburg	0	------	0	1	4	1	0	0	1	24	20
Norfolk	0	8	0	0	2	0	0	0	0	0	19
Richmond	0	------	2	0	4	5	0	4	0	0	64
Roanoke	1	------	0	1	4	0	0	2	0	0	31
West Virginia:											
Charleston	1	------	0	0	4	0	0	0	0	0	16
Huntington	2	------	-------	0	-------	0	0	-------	0	0	-------
Wheeling	0	------	0	0	2	1	0	0	0	2	15
North Carolina:											
Gastonia	0	------	-------	0	-------	1	0	-------	0	3	-------
Raleigh	1	------	0	1	0	0	0	0	0	1	7
Wilmington	0	------	0	0	0	0	0	0	0	8	11
Winston-Salem	0	1	1	20	0	1	0	2	0	2	21
South Carolina:											
Charleston	1	48	0	0	4	1	0	1	2	0	31
Greenville	0	------	0	0	3	0	0	1	0	1	28
Georgia:											
Atlanta	2	35	10	0	15	2	0	2	0	1	115
Brunswick	0	------	0	0	0	0	0	0	0	0	3
Savannah	0	2	2	0	2	1	0	1	1	0	30
Florida:											
Miami	0	------	0	0	6	1	0	0	1	2	32
Tampa	1	2	2	9	1	0	0	2	0	0	27
Kentucky:											
Covington	2	------	0	0	3	0	0	2	0	0	20
Lexington	0	------	0	0	3	1	0	0	0	0	23
Louisville	0	1	1	5	9	9	0	2	0	3	50
Tennessee:											
Knoxville	0	2	0	0	1	3	0	1	0	0	23
Memphis	1	------	3	1	8	7	0	4	0	7	83
Nashville	0	------	1	0	3	2	0	2	0	0	76
Alabama:											
Birmingham	1	10	1	1	5	2	0	6	0	0	91
Mobile	0	------	1	0	7	0	0	0	0	0	28
Montgomery	1	11	-------	5	-------	0	0	-------	0	0	-------
Arkansas:											
Fort Smith	1	2	-------	1	-------	3	0	-------	0	0	-------
Little Rock	0	------	0	0	4	2	0	3	0	0	7

City reports for week ended January 7, 1939—Continued

State and city	Diphtheria cases	Influenza cases	Influenza deaths	Measles cases	Pneumonia deaths	Scarlet fever cases	Smallpox cases	Tuberculosis deaths	Typhoid fever cases	Whooping cough cases	Deaths, all causes
Louisiana:											
Lake Charles	1	------	0	0	2	3	0	1	0	0	7
New Orleans	7	5	4	31	21	8	0	7	6	7	162
Shreveport	1	------	0	1	15	4	0	1	2	0	44
Oklahoma:											
Oklahoma City	0	2	--------	1	6	3	0	0	0	0	52
Tulsa	1	------	--------	8	-------	1	0	-------	0	0	--------
Texas:											
Dallas	3	4	4	0	5	6	6	2	0	0	66
Fort Worth	0	------	0	0	7	7	0	1	0	0	33
Galveston	1	------	0	0	3	1	0	0	0	0	17
Houston	7	------	0	0	17	7	1	6	0	0	108
San Antonio	0	------	2	0	15	1	0	10	0	0	79
Montana:											
Billings	0	------	0	92	1	3	0	0	0	1	7
Great Falls	0	------	0	0	2	1	0	0	0	0	5
Helena	0	------	0	1	2	0	0	0	0	0	9
Missoula	0	------	0	0	0	3	0	0	0	0	5
Idaho:											
Boise	0	------	0	1	1	0	0	0	0	0	7
Colorado:											
Colorado Springs	0	------	0	2	2	3	0	2	0	4	13
Denver	8	------	2	0	8	6	0	2	0	35	91
Pueblo	0	------	0	0	4	3	0	2	0	0	13
New Mexico:											
Albuquerque	0	------	0	0	4	1	0	2	0	0	15
Utah:											
Salt Lake City	0	------	0	0	3	7	0	1	0	5	47
Washington:											
Seattle	2	------	1	2	4	9	0	3	0	9	100
Spokane	0	------	0	17	6	2	0	0	0	0	33
Tacoma	0	------	0	1	5	2	0	1	0		40
Oregon:											
Portland	0	1	2	0	1	3	0	0	0	0	73
Salem	0	1	--------	0	-------	4	0	-------	0	0	--------
California:											
Los Angeles	16	9	1	18	30	46	1	12	0	8	366
Sacramento	0	------	0	6	8	0	0	0	0	0	53
San Francisco	2	1	0	407	19	14	1	6	1	6	197

State and city	Meningitis, meningococcus cases	Meningitis, meningococcus deaths	Poliomyelitis cases
New York:			
Buffalo	1	0	0
New York	3	3	0
Indiana:			
Fort Wayne	1	0	0
District of Columbia:			
Washington	1	1	0
Virginia:			
Richmond	1	0	0
South Carolina:			
Charleston	1	0	0
Florida:			
Miami	1	0	0
Tennessee:			
Nashville	2	0	0
Louisiana:			
New Orleans	2	0	0
Shreveport	0	1	0
Idaho:			
Boise	1	1	0
Oregon:			
Portland	0	0	1
California:			
Los Angeles	2	2	0

Encephalitis, epidemic or lethargic.—Cases: New York, 2; Columbus, 1; Muncie, 1; Kansas City, 1.
Pellagra.—Cases: Atlanta, 7; Birmingham, 1; Oklahoma City, 1.
Typhus fever.—Cases: New York, 1; Charleston, S. C., 3; Atlanta, 1; Savannah, 1; Shreveport, 1.

FOREIGN AND INSULAR

ITALY

Communicable diseases—4 weeks ended November 6, 1938.—During the 4 weeks ended November 6, 1938, cases of certain communicable diseases were reported in Italy as follows:

Disease	Oct. 10–16	Oct. 17–23	Oct. 24–30	Oct. 31–Nov. 6
Anthrax	32	22	32	25
Cerebrospinal meningitis	7	14	21	13
Chickenpox	124	97	93	97
Diphtheria	571	627	576	686
Dysentery	57	41	38	36
Hookworm disease	6	28	25	21
Lethargic encephalitis	1	2	1	
Measles	349	340	357	496
Mumps	51	54	71	80
Paratyphoid fever	169	148	157	114
Pellagra	2	2	4	1
Poliomyelitis	57	80	66	48
Puerperal fever	29	31	30	31
Rabies			1	
Scarlet fever	258	317	266	275
Typhoid fever	1,113	1,040	841	817
Undulant fever	31	37	42	29
Whooping cough	137	183	171	184

SWEDEN

Communicable diseases—October 1938.—During the month of October 1938, cases of certain communicable diseases were reported in Sweden as follows:

Disease	Cases	Disease	Cases
Cerebrospinal meningitis	1	Poliomyelitis	[1] 282
Diphtheria	18	Scarlet fever	2,339
Dysentery	4	Syphilis	44
Epidemic encephalitis	1	Typhoid fever	17
Gonorrhea	1,151	Undulant fever	9
Paratyphoid fever	15	Weil's disease	4

[1] Includes 69 cases nonparalytic at time of notification.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER

From medical officers of the Public Health Service, American consuls, International Office of Public Health, Pan American Sanitary Bureau, health section of the League of Nations, and other sources. The reports contained in the following table must not be considered as complete or final as regards either the list of countries included or the figures for the particular countries for which reports are given.

CHOLERA

[C indicates cases; D, deaths; P, present]

Place		May 29–June 25, 1938	June 26–July 30, 1938	July 31–Aug. 27, 1938	Aug. 28–Sept. 24, 1938	Week ended— October 1938: 1	8	15	22	29	November 1938: 5	12	19	26	December 1938: 3	10	17	24
Afghanistan: [1] Kabul	C											18						
China:																		
Amoy	C													7				
	D													3				
Canton	C	2	16	13	19	5	7											
	D		5	2	4													
Foochow	C				95		8		29	3	17	17	20					
	D				41		6		14	1	2	1						
Hankow	C	24	213	162	73	2												
Hong Kong	C	22	202	128	68	7	9	16	7	7	7	8	7	7	2	3	1	
	D	7	158	54	42			7	9	5	5	2	11	2	3	2	1	
Kwangtung Province	C		11,295	2,581	2,870	142												
	D		2,724	696	752	26												
Macao	C	49	557	182	113	7	18	39	33	15	21	14	1	7	1			
	D		399	127	41							6	1	3	1			
Mukden	C			P														
Shanghai	C	482	2,053	3,876	988	113	95	82	87	24	15	10	5	2		6		4
Swatow	C	710	518	27	37	3	5	4		7		7						
Tientsin	C		9	28	5													
Tsingtao	C			P														
Yunnanfu.[2]																		
Chosen (Korea)	C				47	2												
	D				27	1												
India	C	47,910	48,514	55,794	45,668	8,807	6,680	6,791	6,196	5,922	2,701	2,710						
	D	23,687	22,283	25,767	20,788	4,314	3,297	3,585	3,229	3,144	1,423	1,519						
Allahabad	C	5	18	5									2					
Assam	C	1,194	530	236	1,093	431	211	256	909	446	465	757	1,014	1,319	1,046	629		
	D	575	296	101	555	192	112	147	194	276	237	439	566	738	720	452		
Bassein	C	4																
Bengal Presidency	C		1,281	728	4,598	2,006	1,692	1,671	1,786	2,288	2,645	2,932	3,450	3,526	3,741	3,066		
	D		587	362	2,288	1,048	835	959	943	1,263	1,541	1,671	2,015	1,948	2,177	1,778		
Bombay Presidency	C	154	767	2,123	1,478	248	267	381	330	270	324	250	257	206				
	D	81	277	749	684	126	95	161	141	140	136	105	122	89				
Bombay	C	1		3														
Calcutta	C	343	144	70	89	7	39	24	21	23	20	34	41	41	34	38	20	

[1] Cholera also reported present early in June in South Afghanistan, Afghanistan.

[2] Information dated Nov. 30, 1938, stated that cholera had appeared in villages near Yunnanfu, China. In one village of approximately 1,000 persons, 500 were said to have died.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued

CHOLERA—Continued

[C indicates cases; D, deaths; P, present]

Place		May 29–June 25, 1938	June 26–July 30, 1938	July 31–Aug. 27, 1938	Aug. 28–Sept. 24, 1938	Week ended— October 1938 1	8	15	22	29	November 1938 5	12	19	26	December 1938 3	10	17	24
India—Continued.																		
Cawnpore	C	88	202	101	26	1	1	1	1	------	------	------	------	------	------	------	------	------
	D	33	49	34	8	------	1	------	------	------	------	------	------	------	------	------	------	------
Central Provinces and Berar	C	6,878	14,427	27,998	24,285	3,463	1,670	1,455	862	578	418	391	240	86	102	57	28	------
Chittagong	C	1	2	3	------	------	------	------	------	------	------	------	------	------	------	1	------	------
Delhi	C	64	14	1	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Howrah	C	127	156	103	137	26	23	37	25	15	5	------	------	------	------	------	------	------
Madras Presidency	C	1,169	3,613	1,898	1,842	525	403	370	212	153	116	66	45	------	------	------	------	------
	D	475	1,501	850	731	228	190	153	100	62	47	33	20	------	------	------	------	------
Madras	C	2	3	2	2	------	------	3	1	------	1	2	1	------	1	------	1	------
	D	------	------	------	------	------	------	1	1	------	------	------	2	------	------	------	------	------
Negapatam	C	------	------	------	------	------	------	------	------	------	------	2	3	------	1	4	------	------
	D	------	------	------	------	------	------	------	------	------	------	1	------	------	------	2	------	------
Northwest Frontier Province	C	555	419	468	114	12	6	6	2	------	6	------	------	------	------	------	------	------
Orissa Province	C	332	233	52	12	3	1	6	8	15	------	1	1	------	------	15	------	------
Gopalpur	C	5	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Punjab	C	673	542	88	15	------	------	------	------	------	------	------	------	------	------	------	------	------
Rangoon	C	1	------	------	1	------	1	------	------	------	------	------	------	------	------	------	------	------
Sind State	C	242	221	61	1	------	------	------	------	------	------	------	------	------	------	------	------	------
India (French):																		
Chandernagor Territory	C	11	8	------	1	------	------	------	------	------	------	1	------	------	------	------	------	------
Karikal Territory	C	------	------	------	------	------	------	------	------	1	------	------	------	------	------	------	------	------
Pondichery Province	C	2	------	------	------	------	------	3	------	------	------	------	------	------	------	------	------	------
Yanaon	C	------	2	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------
India (Portuguese): Damao	C	------	------	------	7	------	------	------	------	------	------	------	------	------	------	------	------	------
Indochina (French):																		
Annam Province	C	698	923	440	35	------	------	------	7	------	------	------	------	------	------	------	------	------
Tonkin Province	C	1,383	451	23	7	------	61	15	1	------	------	------	------	------	------	------	------	------
Hanoi	C	82	34	4	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Japan:																		
Fukuoka Prefecture—Wakamatsu	C	------	2	------	------	3	------	------	------	------	------	------	------	------	------	------	------	------
Hiroshima Prefecture—Fukuyama	C	------	------	------	------	3	------	------	------	------	------	------	------	------	------	------	------	------
Okayama Prefecture	C	------	8	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------
	D	------	4	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------

On vessels:

S. S. *Tak Sang* at Hong Kong from Shanghai and Swatow—1 case—June 5, 1938
S. S. *Kikukawa Maru* at Fukuoka from Shanghai—57 cases—July 28, 1938
S. S. *Mau Sang* at Hong Kong from Sandakan—1 case—July 18, 1938

On vessels—Continued.

S. S. *Kweiyang* at Bangkok from Swatow and Hong Kong—1 case—Aug. 5, 1938
S. S. *Ethiopia* at Madras—1 case—Sept. 5, 1938

PLAGUE [1]

[C indicates cases; D, deaths; P, present]

Place		May 29–June 25, 1938	June 26–July 30, 1938	July 31–Aug. 27, 1938	Aug. 28–Sept. 24, 1938	Week ended— October 1938 1	8	15	22	29	November 1938 5	12	19	26	December 1938 3	10	17	24
Argentina. (See table below.)																		
Belgian Congo	C	2	3	3	1										1			
Bolivia (see also table below):																		
Santa Cruz Department	C	10																
Tarija Department	C	96																
Brazil. (See table below.)																		
British East Africa:																		
Kenya	C		9	4	2		1								1			
Uganda	C	19	59	45	53		9	23	16	15	14	4	9		4	3		
	D	17	61	44	50		9	23	15	15	14	4	8		4	3		
Ceylon:																		
Colombo	C	1		1														
	D	1		1														
Plague-infected rats		1	1	2														
China. [2]																		
Dutch East Indies: Java and Madura	C	135	157	120	120	19	31	42										
	D	135	157	120	120	19	31	39										
Ecuador: Guayaquil	C		1								1	1						
	D										1	1						
Plague-infected rats												3						
Egypt: Asyut Province	C	1																
Hawaii Territory: Plague-infected rats:																		
Hawaii Island—Hamakua District									1	5								
Hamakua Mill Sector [3]												2	3	8		[4] 23		10
Paauhau Sector				1			2	1	4	3	5		4	3	4			5
India	C	68	488	907	1,223	450	320	506	351	512	406	453						
	D	32	275	409	498	200	182	211	157	225	171	156						
Bassein	C	2	4	2	2													
Plague-infected rats			1											1				
Bombay Presidency	C	11	27	49	83	21	12	13	13	47	30	33	35	33				
	D	9	14	27	40	20	8	4	8	23	15	14	15	21				
Central Provinces and Berar	C	1		126	412	166	46	144	73	155		186	146	98	181	215	90	

[1] Including plague in the United States and its possessions.

[2] According to information dated Aug. 12, 1938, 23 deaths from plague occurred in Kirin Province, China, up to Aug. 10, 1938, and 16 deaths from plague occurred in South Hin An Province from July 28 to Aug. 8. Information dated Aug. 25, 1938, states that 17 cases of plague had occurred in South Hsingan Province and that 10 cases of plague with 10 deaths were reported in Northern Kirin Province between July 29 and Aug. 10.

[3] For the week ended Dec. 31, 1938, 7 plague-infected rats were reported in Hamakua Mill Sector, Hamakua District, Island of Hawaii, T. H.

[4] For 2 weeks.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued

PLAGUE—Continued

[C, indicates cases; D, deaths; P, present]

Place		May 29–June 25, 1938	June 26–July 30, 1938	July 31–Aug. 27, 1938	Aug. 28–Sept. 24, 1938	Week ended— October 1938: 1	8	15	22	29	November 1938: 5	12	19	26	December 1938: 3	10	17	24
India—Continued.																		
Cochin	C			1						1			2					
	D			1									2					
Plague-infected rats				2	10	3	2	4	2	2	1	2	1	2	2		1	
Madras Presidency	C	51	231	227	195	52	48	119	86	77	48	61	66					
	D	24	84	97	88	27	21	42	31	35	29	23	29					
Rangoon	C	1	3	1	2													
	D	1	3	1	2													
Madagascar. (See table below.)																		
Peru. (See table below.)																		
Senegal: M'Bour subdivision	C	1																
Tunisia: Tunis	C							1	1			1	1			2		
Plague-infected rats			2								1							
Union of South Africa (see also table below)	C	8	4		3													
Cape Province—Port Elizabeth	C	2	3	2	1	1												
	D		1															
United States.[1]																		

Place		June 1938	July 1938	August 1938	September 1938	October 1938	November 1938
Argentina: Salta Province	C	4		1	1		
Bolivia (see also table above)	C		6	4	[2] 103		
Brazil: Pernambuco State	C			4			
Madagascar (central region)	C	5	22	33	60	70	
	D	5	20	31	60	64	

Place		June 1938	July 1938	August 1938	September 1938	October 1938	November 1938
Peru	C		1	4	7	6	
Libertad Department	C			1			
Lima Department	C		1	3	6	6	
Union of South Africa: Orange Free State	C	5					

[1] Last reported human case, Aug. 30, 1937, Fresno County, Calif. Intensive plague work is being conducted in the Western States and detailed reports of plague-infection found in animals and insect hosts are published currently in the PUBLIC HEALTH REPORTS. The following summarizes recent reports for 1938: *Arizona*—Insects, Sept. 27; *California*—Ground squirrels, June, July, August, October, Dec. 11; insects, June, July, August, October, Dec. 22; *Idaho*—Ground squirrels, June; insects, June, July; *Montana*—Ground squirrels, June; insects, June; *New Mexico*—Prairie dogs, August, September; insects, August, September; *Utah*—Ground squirrels, June; insects, July; *Wyoming*—Ground squirrels, June, July; insects, June, July, August.

[2] For the period Sept. 8–Oct. 7, 1938.

SMALLPOX

[C indicates cases; D, deaths; P, present]

Place		May 29–June 25, 1938	June 26–July 30, 1938	July 31–Aug. 27, 1938	Aug. 28–Sept. 24, 1938	Week ended— October 1938 1	8	15	22	29	November 1938 5	12	19	26	December 1938 3	10	17	24
Algeria:																		
Algiers Department	C	1							1									
Constantine Department	C	1		1														
Philippeville	C			1														
Angola. (See table below.)																		
Belgian Congo. (See table below.)																		
Bolivia. (See table below.)																		
Brazil. (See table below.)																		
British East Africa: Tanganyika	C	84	158	94	30	27	9	1		1	19	13	14					
Canada:																		
Alberta	C	12	[1] 1															
Manitoba	C	16	[1] 10															
Ontario	C			9					1				2				[1] 1	
Saskatchewan	C		[1] 11		[1] 1				[1] 2		[2] 3		[2] 6				[1] 3	
China:																		
Amoy	C										1	1						
Dairen	C	2													1			
Hankow	C	24	6			1												
Hong Kong	C	25	5									1	1		3	1	9	11
	D	19	3													5	4	8
Shanghai	C	8	7	7	4	6	12	10	8	17	38	82	64	144	222	211	339	297
Tientsin	C	1																
Chosen (Korea). (See table below.)																		
Colombia (see also table below): Cartagena	D	1	1															
Dahomey. (See table below.)																		
Dutch East Indies:																		
Batavia	C				[2] 1													
Surabaya	C																[2] 1	
Ecuador: Guayaquil. (See table below.)																		
France. (See table below.)																		
Great Britain: England and Wales—																		
Kent County—Gravesend	C	1																
Lancaster County	C		2	3														
York County	C													3				

[1] For 2 weeks.
[2] Imported.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued

SMALLPOX—Continued

[C indicates cases; D, deaths; P, present]

Place		May 29–June 25, 1938	June 26–July 30, 1938	July 31–Aug. 27, 1938	Aug. 28–Sept. 24, 1938	Week ended— October 1938 1	8	15	22	29	November 1938 5	12	19	26	December 1938 3	10	17	24
Greece. (See table below.)																		
Guatemala. (See table below.)																		
India	C	5,716	4,562	1,635	1,206	264	161	269	274	257	276	260	------	------	------	------	------	------
	D	1,621	1,242	510	330	43	35	62	62	57	50	67	------	------	------	------	------	------
Assam	C	163	87	49	10	4	4	------	------	25	6	4	20	9	16	5	3	28
Bassein	C	------	1	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Bengal Presidency	C	------	389	166	123	22	12	25	46	41	28	26	51	55	58	54	74	------
	D	------	132	59	51	3	7	7	17	15	7	3	4	15	12	7	20	------
Bombay Presidency	C	826	684	401	281	98	61	96	76	30	46	30	114	24	------	------	------	------
	D	170	119	77	37	10	4	17	12	8	7	1	14	5	------	------	------	------
Bombay	C	57	37	15	9	------	3	1	1	------	------	------	------	------	------	------	1	------
	D	38	28	11	3	------	------	------	------	------	------	------	------	------	------	------	1	------
Calcutta	C	165	86	31	28	------	1	3	5	1	4	6	14	18	10	17	30	24
	D	142	54	23	18	------	1	------	5	1	1	3	4	9	6	5	21	18
Cawnpore	C	2	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Central Provinces and Berar	C	260	144	28	15	1	7	1	5	------	------	3	------	------	2	21	12	11
Cochin	C	------	------	------	------	------	------	------	------	------	------	------	------	------	------	1	------	------
Delhi	C	8	1	------	1	------	------	------	------	------	------	1	1	3	5	1	3	10
Howrah	C	50	24	17	27	5	3	3	------	7	5	------	------	------	------	------	------	------
Jodhpur	C	1	------	------	1	------	------	------	------	------	------	------	------	------	------	------	------	------
Karachi	C	4	------	1	------	------	------	------	------	------	------	------	------	[2]1	------	------	------	------
Madras Presidency	C	228	539	511	306	58	40	55	71	57	79	93	80	------	------	------	------	------
	D	44	113	98	64	11	5	9	16	9	5	24	10	------	------	------	------	------
Madras	C	126	185	132	100	14	16	17	26	8	22	50	26	62	32	49	32	29
Moulmein	C	------	------	------	------	------	------	------	------	------	------	------	------	4	------	------	------	------
Northwest Frontier Province	C	82	95	75	24	4	8	5	12	8	16	17	15	27	68	56	99	44
Orissa Province	C	487	442	258	119	3	14	6	8	15	7	14	1	13	30	34	47	63
Punjab	C	44	41	16	13	1	3	2	2	2	------	5	32	20	40	13	16	49
Rangoon	C	21	2	6	4	1	------	------	2	------	1	1	2	1	------	------	------	1
Sind State	C	300	167	112	63	------	------	13	3	13	49	14	18	38	40	59	94	22
India (French): Chandernagor Territory	C	2	------	3	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Indochina (French) (see also table below):																		
Tonkin Province	C	156	88	45	46	5	9	8	12	------	12	35	17	31	35	41	23	99
Haiphong	C	1	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Hanoi	C	4	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Saigon-Cholon	C	------	5	3	7	5	4	------	------	------	------	------	------	------	2	------	------	2

Iran	C			1		3												
Iraq	C				3												1	
Ivory Coast. (See table below.)																		
Japan:																		
Kobe	C	1														1	2	
Nagasaki	C														5			
Nara Prefecture	C	1																
Okayama Prefecture	C												1					
Lithuania. (See table below.)																		
Mexico (see also table below):																		
Mexico, D. F	C	8	7	1														
Monterrey	C	5		3														
Saltillo	D	1																
San Luis Potosí	D	1																
Tampico	C												1					
Morocco. (See table below.)																		
Nigeria	C	130	102	280					156		87							
Lagos	C	2	2	1	13		5	1	1									
Niger Territory. (See table below.)																		
Northern Rhodesia	C		22	6	6				2	7						2		
Nyasaland	C			1	6		2	1										
Portugal (see also table below):																		
Lisbon	C	6	7	5	5	2	2	1		3	4	5	8	3		2	2	1
Oporto	C				1	2	5			3						3		
Salvador. (See table below.)																		
Siam	C	1			33													2
Sierra Leone	C	1	1															
Southern Rhodesia	C	70	983	403	97	9	2	40	4	2	33	54	23	15				
Sudan (Anglo-Egyptian)	C	8	1	4	2	20	2	1	4	3		10	9	1	12	6	1	7
Tunisia: Tunis	C	3																
Union of South Africa. (See table below.)																		
Uruguay. (See table below.)																		
Venezuela. (See table below.)																		

On vessels:

S. S. *Ellenga* at Rangoon from Calcutta	1 case	July 19, 1938
S. S. *Planter* at Aden	1 case	Aug. 2, 1938
S. S. *Pronto* at Tangku-Taku from Hong Kong	1 case	Aug. 8, 1938
S. S. *Defender* at Aden	1 case	Aug. 19, 1938
S. S. *Katori Maru* at Kobe from London, Singapore, Hong Kong, and Shanghai	3 cases	Aug. 20, 1938

On vessels—Continued.

S. S. *Conte Biancamano* at Suez from Shanghai, Colombo, Bombay, and Massowah	1 case	Sept. 10, 1938
S. S. *Hartlebury* bound for New York via Durban [3]	1 case	Dec. 1, 1938
S. S. *Westpoint* at sea en route Surabaya	1 death	Dec. 10, 1938
S. S. *Tyles* at Yokahama from Hong Kong and Shanghai	1 case	Dec. 13, 1938

[2] Patient removed from vessel and died in hospital in Iloilo district, P. I.
[3] Imported.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued

SMALLPOX—Continued

[C indicates cases; D, deaths; P, present]

Place		June 1938	July 1938	August 1938	September 1938	October 1938	November 1938
Angola	C		35	62			
Belgian Congo	C		262	163	185	354	
Bolivia:							
Cochabamba Department	C	4	2	[4] 2	[5] 1		
Chuquisaca Department	C			[4] 3			
La Paz Department	C	5	5	[4] 27	[5] 16		
Oruro Department	C				[5] 4		
Potosi Department	C	4	2				
Santa Cruz Department	C	1	5	[4] 8	[5] 7		
Tarija Department	C						2
Brazil:							
Bahia	C			1			
Porto Alegre	C			1			
Chosen (Korea)	C		4				
Colombia	C	[6] 226	124	68	60		
Dahomey	C			16			
Ecuador: **Guayaquil** and vicinity	C				3		6
France	C				1		
Greece: **Salonika**	C		5				
Guatemala	C	4		1			16
Indochina (French) (see also table above)	C		409	206	113	166	
	D		89	48	35	25	

Place		June 1938	July 1938	August 1938	September 1938	October 1938	November 1938
Ivory Coast	C			10			
Lithuania	D			1			
Mexico (see also table above):							
Aguascalientes State—Aguascalientes	C				2	6	
Colima State	C				1		
Hidalgo State	C					30	
Mexico, D. F	C			1	2		
Nuevo Leon State—Monterrey	C			3			
Queretaro State	C			16	3		
Sonora State	C			1			
Morocco	C	3	4	1			3
Portugal (see also table above)	C	41		40	78	72	
	D	2		4	3	7	
Salvador	C					1	
Union of South Africa:							
Cape Province	C			1	1		
Natal	C			25	1		
Orange Free State	C			1			
Transvaal	C			33	18		
Uruguay—Montevideo	C	2					
Venezuela	D	5	2	3	3	1	

[4] For the period Aug. 1 to Sept. 7, 1938.
[5] For the period Sept. 8 to Oct. 7, 1938.
[6] For 3 months.

TYPHUS FEVER

[C indicates cases; D, deaths; P, present]

Place		May 29–June 25, 1938	June 26–July 30, 1938	July 31–Aug. 27, 1938	Week ended—														
					September 1938				October 1938					November 1938				December 1938		
					3	10	17	24	1	8	15	22	29	5	12	19	26	3	10	17
Algeria:																				
Algiers Department	C	53	13	5	1	----	1	----	1	5	----	----	----	1	1	3	1	7	----	13
Algiers	C	4	----	----	----	----	----	----	----	----	----	----	----	----	----	3	----	5	----	----
Constantine Department	C	172	42	20	9	2	5	9	3	2	----	----	3	----	2	1	3	5	17	11
Bone	C	26	3	4	----	----	----	----	1	----	----	----	----	----	1	----	----	----	----	----
Constantine	C	5	5	1	----	----	1	----	----	----	----	----	----	----	1	----	----	----	3	----
Philippeville	C	----	----	7	2	1	1	7	----	----	----	----	3	1	----	----	----	3	----	----
Oran Department	C	18	9	12	----	1	----	----	----	1	----	----	4	4	----	----	----	----	----	----
Australia: Adelaide	C	----	1	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Basutoland	C	----	2	3	----	1	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Belgium. (See table below.)																				
Bolivia. (See table below.)																				
British East Africa: Kenya	C	----	----	3	1	1	----	----	----	----	----	----	----	3	----	----	----	----	----	----
Bulgaria	C	----	4	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Chile	C	23	43	40	35	16	11	19	12	5	13	23	19	----	----	----	----	----	----	----
Antofagasta Province	C	----	----	----	----	----	----	----	----	2	----	----	3	----	----	----	----	----	----	----
Concepcion	C	1	3	----	----	----	----	----	1	----	----	----	----	----	----	----	----	----	----	----
Coquimbo Province	C	----	8	1	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Llanquihue Province	C	----	----	----	15	----	----	1	----	----	----	----	----	----	----	----	----	----	----	----
Malleco Province	C	2	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Nuble Province	C	10	10	16	2	----	4	4	1	----	----	----	----	----	----	----	----	----	----	----
Santiago Province	C	1	4	14	17	16	6	----	8	5	----	----	18	----	----	----	----	----	----	----
Tarapaca Province	C	----	10	1	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Valdivia Province	C	----	1	1	----	----	----	4	2	----	----	----	----	----	----	----	----	----	----	----
Valparaiso	C	6	3	1	----	----	1	1	----	----	3	1	----	2	----	1	1	----	----	1
China (see also table below):																				
Dairen	C	6	1	----	----	----	----	----	----	----	----	----	----	1	----	----	----	----	----	----
Shanghai	C	214	62	----	5	----	----	3	2	3	----	----	2	----	----	----	----	----	----	----
Chosen (Korea). (See table below.)																				
Colombia: Barranquilla	D	----	1	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Czechoslovakia. (See table below.)																				
Egypt:																				
Alexandria	C	5	3	1	----	----	1	----	----	----	----	----	----	----	----	----	----	----	----	----
Aswan Province	C	4	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Asyut Province	C	1	2	2	1	1	----	----	----	----	----	----	----	----	----	----	----	----	----	----

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued

TYPHUS FEVER—Continued

[C indicates cases; D, deaths; P, present]

Place		May 29–June 25, 1938	June 26–July 30, 1938	July 31–Aug. 27, 1938	Week ended—														
					September 1938				October 1938					November 1938				December 1938		
					3	10	17	24	1	8	15	22	29	5	12	19	26	3	10	17
Egypt—Continued																				
Beheira Province	C	45	10	6	7	3														
Cairo	C	24	8	2			1													1
Dakahliya Province	C	10	29																	
Gharbiya Province	C	23	4	6	3	3		2		8										
Girga Province	C		5	1	3	1		1		1										
Giza Province	C		22	1																
Kalyubiya Province	C		7	1																
Minufiya Province	C	33	27																	
Minya Province	C			1								1								
Qena Province	C	1																		
Sharkiya Province	C	8	7					1												
Provinces	C	414	245	95	14	9	2	3	9	1	4	18			2	1	5			18
Greece. (See table below.)																				
Guatemala. (See table below.)																				
Hawaii Territory: Honolulu	C	2	3	3	1	1		2	2	1	2			3	2	3		3	1	
Hungary	C		1																	1
Iran	C														1					
Iraq	C			1				3	1									1		1
Latvia. (See table below.)																				
Libya: Garian	C			1																
Lithuania. (See table below.)																				
Mexico (see also table below):																				
Guadalajara	D																	1		
Mexico, D. F.	C	7	15	1	4		2			2	2	4	2	2	2	5	1			
Monterrey	C								1											
Nuevo Laredo	D																2			
Torreon	D			2					1											
Morocco	C	576	226	55	4	3	4			4		2	3	16		39	27		41	20
Casablanca	C	34	23	5																
Palestine:																				
Haifa	C	3			1		2		1		1	1			1	1		1		
Jaffa	C	2	2	4		3		6	3		1	4	1						3	
Poland	C	267	215	58	12	5	12	8	10	17	14	7	15	18	24	25	27	67	43	47
	D	12	9					1		1			2	3	1	1	1	2	1	5
Portugal. (See table below.)																				

Rumania. (See table below.)																					
Sierra Leone: Freetown	C	1																			
Straits Settlements: Singapore	C	1	1	1											1						
Syria:																					
Beirut	C												1								
Lebanese Republic	C											1									
Trans-Jordan	C											1				1					
Tunisia:																					
Tunis	C	15	11	3			1	8	4	8		2	5	3	5	3		32			
Provinces	C	349	245	86	18	20	18	17	5	19		9	7			12			49	117	
Turkey. (See table below.)																					
Union of South Africa. (See table below.)																					
Yugoslavia	C	60	34	11	1		1	5	8	1		2	3		2	2	1	3	16		

Place		June 1938	July 1938	August 1938	September 1938	October 1938	November 1938
Belgium: Brussels	C				2		
Bolivia:							
Cochabamba Department	C		1	[1]1			
La Paz Department	C	8	5		[2]6		[3]14
La Paz	C		2	[1]1	[2]3		[3]11
Oruro Department	C	6	2	[1]1	[2]1		[3]3
Potosi Department	C	4	3	[1]7			
China: Manchuria—Harbin	C		1	2	5	2	16
Chosen (Korea)	C		22	1	12		
Czechoslovakia	C			3			
Greece	C		5			4	
Guatemala	C	11	108	20	6	3	38
Latvia	C		1				
Lithuania	C	3	3				
Mexico (see also table above):							
Aguascalientes State—Aguascalientes	C					1	
Hidalgo State	C			4	1	5	
Jalisco State—Guadalajara	C				1		

Place		June 1938	July 1938	August 1938	September 1938	October 1938	November 1938
Mexico (see also table above)—Con.							
Mexico State	C				4	6	
Mexico, D. F	C			5	10	10	
Oaxaca State	C					2	
Puebla State—Puebla	C				1	2	
Queretaro State	C			1	1	1	
San Luis Potosi State—San Luis Potosi	C				1	2	
Tamaulipas State	C			1			
Portugal	C		3	2	2		
Rumania	C	35	10	5	8	27	
Turkey	C		12		17	13	21
Istanbul	C	6	4	2	5	2	2
Union of South Africa:							
Cape Province	C	37	98	62	165		
Natal	C		1	1	4		
Orange Free State	C	2	10		7		
Transvaal	C			1			

[1] For the period Aug. 1 to Sept. 7, 1938.
[2] For the period Sept. 8 to Oct. 7, 1938.
[3] For the period Oct. 8 to Nov. 30, 1938.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued

YELLOW FEVER

[C indicates cases; D, deaths; P, present]

Place		May 29–June 25, 1938	June 26–July 30, 1938	July 31–Aug. 27, 1938	Week ended— September 1938				October 1938					November 1938				December 1938		
					3	10	17	24	1	8	15	22	29	5	12	19	26	3	10	17
Brazil:[1]																				
Amazonas State	D		1																	
Minas Geraes State	D	3																		
Colombia: Cundinamarca Department	D	3	2	2																
Dahomey: Allada	C		1																	
French Equatorial Africa:																				
Gabon—Koula Moutou	C		[2]1																	
Sosso	C														1					
Gold Coast	C	3	3		1			2		1	3									
	D		1		1					1										
Ivory Coast	C		[2]1							2	1				[2]2	[2]3	[3]3	[2]2		[3]3
	D			1																2
Nigeria	C			[2]2	1					1					1	2	1		[2]1	
	D			[2]1																
Port Harcourt	C																1			
Sudan (French):																				
Kona	C							[2]1									[2]1	3		
Kouy	C																			
Sangha	C																		1	
Segou Circle—Kokry	C	1																		
Tougan	C										3									
On vessel: S. S. *St. Octave* at Grand Bassam Roadstead from Bordeaux, Dakar, Konakry, Tabou, and Sassandra	C																[3]	1		

[1] See also reports of yellow fever in Brazil in preceding issues of the PUBLIC HEALTH REPORTS.
[2] Suspected.
[3] Includes 1 suspected case.