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STUDIES ON THE PHARMACOLOGIC ACTION AND THE PATHOLOGY OF ALPHANAPHTHYLTHIOUREA (ANTU)

I. PHARMACOLOGY [1]

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The investigations by Richter and associates (*1*) of phenylthiocarbamide taste thresholds in rats and humans led them to study the toxic effects of this substance in rats with the interesting observation that it was capable of producing in relatively small doses large serous effusions in the thoracic cavity, and that repeated administration of the drug in progressively larger amounts induced a considerable degree of tolerance (*2*, *3*). Further unpublished investigations of this and related compounds led him to suggest that alphanaphthylthiourea, which for brevity will be referred to as ANTU, might be used advantageously as a rodenticide. The purpose of this report is to record some of our observations on the toxicology and the pharmacologic action of ANTU in several species of laboratory animals under conditions of acute, subacute, and chronic poisoning.

EXPERIMENTS IN RATS

The acute toxicity of ANTU in rats was determined by administering the substance in gum acacia suspension by stomach tube. Albino rats of the Wistar strain were used throughout. Animals of both sexes, weighing 125 to 200 gm., kept on a stock diet of Purina dog chow, were used. Groups of 10 were used in each experiment. The results of a total of 170 rats given graded doses of ANTU shown in table 1 indicate slightly over 18 percent mortality at a dose level of 20

TABLE 1.—*Acute toxicity of ANTU in rats, oral administration, stock diet*

Dose (mg. per kg.)	Number	Mortality, percent	Average	Dose (mg. per kg.)	Number	Mortality, percent	Average
	10	0			10	80	
	10	60		50	10	30	70
	10	20			10	100	
20	10	30	18.3		10	30	
	10	0		75	10	80	70
	10	0			10	100	
	10	30		100	10	100	100
35	10	50	61		10	100	
	10	100					

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

mg. per kg., 60 to 70 percent mortality at the dose levels of 35 to 75 mg. per kg. and 100 percent mortality at 100 mg. per kg. Symptoms of labored respiration and muscular weakness developed in about 6 hours, and death occurred in from 7 to 36 hours. All animals that came to autopsy showed profuse, clear, straw-colored fluid in the pleural cavity, frequently a small amount of clear fluid in the pericardium, but no other effusions. Animals killed after a survival period of 72 hours or longer gave no evidence of effusions, and it is not known whether fluid was never formed or whether fluid had formed and was reabsorbed.

Examination of the pleural and pericardial effusions for protein content by the refractometric method of Sunderman (*4*) indicated an average of from 3.3 to 4.2 percent at the different dose levels, with no definite relationship between the protein content and drug dosage. No experiments were made to determine whether the protein is chiefly albumin, globulin, or a combination of both.

Attempts to induce chronic ANTU poisoning in rats by incorporating the substance at a level of 0.1 percent in a semisynthetic diet were unsuccessful. The animals refused the food, deteriorated rapidly, and died for the most part of inanition in from 5 to 30 days. No characteristic pathology was to be found in such animals, except in the few that died within 1 to 5 days, which usually showed the typical hydrothorax.

Tolerance was readily induced in rats on the stock diet by administering to the survivors progressively increasing doses of ANTU at 3- to 4-day intervals. In this manner the mortality from 50 mg. per kg., which in the nontolerant animals was 70 percent, was reduced to zero in one series, and 17 percent in another; and a dose of 100 mg. per kg., which in the nontolerant animals gave 100 percent mortality, gave no deaths in one series and 42 percent in another. Death following large doses in tolerant animals was often delayed, and effusions were strikingly absent even in animals dying within 24 hours, though the lungs were usually edematous and hemorrhagic. The livers in some of these animals showed varying degrees of fatty degeneration. The experimental data on induced tolerance in rats are summarized in table 2, and indicate that they may withstand five to six times the dose for normal nontolerant animals. The absence of effusions would seem to suggest an altered mode of action of the drug in the tolerant animal.

In an effort to shed some light on the mechanism of tolerance and the apparent variation in individual susceptibility as revealed in the data of table 1, experiments were made to determine whether dietary deficiency or liver injury induced by dietary means or hepatotoxic agents would have any effect on the acute toxicity of ANTU. Accordingly groups of rats were kept for periods varying from 18 to 175 days

TABLE 2.—*Tolerance to ANTU induced in rats on stock diet*

Dose (mg. per kg.)	Days between doses	Number of animals	Mortality (percent)	Dose (mg. per kg.)	Days between doses	Number of animals	Mortality (percent)
Series 1:				Series 2:			
10	0	20	5	20	0	20	30
20	3	19	0	50	4	14	0
35	3	19	0	75	3	14	0
50	4	[1] 23	17	100	3	14	0
100	3	19	42	200	3	14	70
200	4	10	80	300	3	5	80

[1] 19 survivors in this series plus 4 from another series similarly treated.

on the respective experimental diets and then were tested for susceptibility to a standard dose of ANTU. The diets consisted of casein, 5 percent, dried brewers' yeast to supply the vitamins of the B group, 4 percent salt mixture, 2 percent cod liver oil, 8 percent olive oil and starch. Variations in the protein and fat content were made by corresponding changes in the starch content.

Table 3 summarizes the results of this study. Ten milligrams per kilogram of ANTU was chosen as the standard dose since in normal animals on a stock diet it gave an average mortality of 5 percent

TABLE 3.—*Effect of dietary deficiencies and other factors on susceptibility to ANTU in rats*

Diet number	Description of diet	Days	Average weight change (gm.)	Number of animals	Dose (mg. per kg.)	Mortality (percent)
242	18 percent casein adequate control	28	+77	20	10	20
217	4 percent casein	28	+9	35	10	83
217A	4 percent casein + 2 percent cystine	34	+23	35	10	37
228	15 percent yeast + 30 percent lard + 0.5 percent cystine	18	−5	16	10	81
220	5 percent casein + 20 percent lard + 0.5 percent cystine + 1 percent choline	102	+63	12	10	100
211	18 percent casein + 1 percent carbon tetrachloride	175	+96	12	10	50
242A	18 percent casein, 6 daily doses of 1.5 mg. KI subcutaneously per rat	34	+63	14	10	57
230	18 percent casin + 0.5 percent p-aminobenzoic acid	25	+61	20	10	60

(table 2), and any deviation from this in the way of increased susceptibility could readily be ascertained with a considerable degree of accuracy. The data in table 3 indicate that a 10 mg. per kg. dose of ANTU given to animals on a semisynthetic adequate diet gave a mortality of 20 percent. Reduction of the protein to a 4-percent level increased susceptibility, while the addition of 2 percent cystine restored the mortality rate to approximately the same level as that prevailing in animals on the adequate diet. The low protein and high fat diet, No. 228, produced extremely fatty and enlarged livers and gave a high mortality incidence from the standard dose of ANTU,

and this was not corrected by the addition of 1 percent choline, the lipotropic action of which adequately compensated for the high fat content of the diet, since the liver in this group of animals showed no gross abnormalities. The high mortality incidence in the two groups, Nos. 220 and 228, must therefore be ascribed to the low protein rather than the high fat. It would seem that the 0.5 percent cystine supplement in diet No. 220 was insufficient to afford the degree of protection attained with 2 percent cystine in group 217A.

The mortality in group 211 which received 1 percent carbon tetrachloride was somewhat higher than that of the control group 242. The difference is not considered sufficiently great, however, to ascribe an important role to the type of liver injury induced as a factor in altering susceptibility to ANTU poisoning. The livers in this group of animals uniformly showed moderately severe to severe nodular cirrhosis.

Griesbach and associates (*5*) have recently reported a protective action from the subcutaneous injection of potassium iodide against the acute toxicity of thiourea in rats. Since the toxic manifestations of thiourea poisoning in rats resemble those of ANTU we repeated their experiment with potassium iodide as shown in experiment 242A of table 3 but have been unable to obtain results such as they reported for thiourea. The pretreatment with potassium iodide appeared to have increased rather than decreased the susceptibility to ANTU.

Graying of hair in rats ingesting phenylthiocarbamide as reported by Richter (*2*) suggested the possibility of an antagonistic action of p-aminobenzoic acid against ANTU. Accordingly, this substance was fed to rats for a period of 25 days at a concentration level of 0.5 percent in an otherwise adequate diet and at the expiration of the experimental period 10 mg. per kg. ANTU was given. It would appear that the ingestion of p-aminobenzoic acid has failed to afford protection, but, on the contrary, has seemed to increase susceptibility to ANTU.

EXPERIMENTS IN DOGS

A series of 7 dogs was treated with doses of ANTU varying from 25 to 200 mg. per kg., with a view to ascertaining the degree of susceptibility and the mode of action in this species. The results of this experiment are shown in table 4 and indicate that ANTU produces pleural and, to a lesser extent, pericardial effusions in the dog as in the rat, and that the susceptibility of the dog to ANTU is of about the same order of magnitude as that of the albino rat. All but one of the animals died within 18 to 23 hours. One animal, No. 3, survived 50 mg. per kg., but when given the same dose 6 weeks later died within 29 hours and showed, like all the others, copious fluid in the pleural cavity. The effusion protein estimated from specific gravity by the falling-drop method varied from 4.2 to 5.9 percent. The plasma protein of these animals determined by the same method before the ad-

ministration of ANTU gave values varying from 5.9 to 8.4 percent, with an average of 6.9 percent. It is evident that the effusion protein content in the dog is high, more than half that of the plasma protein, and in some cases appears to be as high as 85 percent.

TABLE 4.—*Acute toxicity of ANTU in dogs.—Oral administration*

Dog number	Weight (kg.)	Dose (mg. per kg.)	Hours survived	Pleural effusion protein
2	5.0	200	18	4.56
6	9.0	100	18	4.60
7	4.6	100	18	4.15
5	6.0	50	22	5.44
4	4.6	50	21	5.95
3	5.3	50	Survived [1]	----------
1	10.0	25	23	5.62

[1] At end of 42 days animal was given 50 mg. per kg. and succumbed in 29 hours. The pleural effusion had 5.6 percent protein.

EXPERIMENTS IN RABBITS

The results of the rabbit experiments with ANTU are shown in tables 5 and 6. The oral acute toxicity of ANTU in the rabbit appears to be low. Half a gram per kilogram was tolerated, and 1.0 gm. per kg. usually proved fatal but death was delayed for several days. Pleural effusions under these conditions were infrequent. With a

TABLE 5.—*Acute toxicity of ANTU in rabbits*

Rabbit number	Weight (kg.)		Dose (gm. per kg.)	Plasma protein (percent)		Pleural effusion protein (percent)	Remarks
	Initial	Final		Normal	At death		
1A	2.0	2.1	0.5	----------	6.3	None	Survived, killed 15 days.
2A	2.1	1.8	.5	----------	6.1	None	Do.
1	2.1	1.9	1.0	----------	6.2	None	Do.
2	2.0	----------	1.0	----------	5.4	4.7	Died in 3 days.
3	2.8	2.2	1.0	----------	7.6	None	Sick, killed in 4 days.
4	2.6	2.2	1.0	----------	5.3	1.6	Do.
5	1.9	1.3	1.0	----------	7.8	----------	Died in 10 days.
6	2.4	2.2	1.0	----------	----------	----------	Died in 6 days.
6A	2.6	----------	2.0	6.9	----------	6.6	Died in 18 hours.
7	2.7	----------	2.0	5.8	----------	6.7	Do.
8	2.4	----------	2.0	5.6	7.3	4.4	Sick, killed in 2 days.
9	2.1	1.5	2.0	6.7	5.2	None	Sick, killed in 7 days.
10	2.6	----------	2.0	7.0	----------	6.6	Died in 18 hours.

TABLE 6.—*Chronic toxicity of ANTU in rabbits, 200 mg. per kg. per day*

Rabbit number	Weight (kg.)		Number of doses	Died or survived	Plasma protein (percent)			Pleural effusion protein (percent)
	Initial	Final			Normal	Second day	Sixth day	
1	2.9	2.4	[1] 3½	Died	7.0	7.9	----------	None.
2	1.8	1.6	5½	----do	6.8	7.9	4.6	Do.
3	1.9	1.9	2½	----do	6.7	----------	----------	3.4.
4	2.5	2.2	4½	----do	6.5	7.9	----------	None.
5	3.3	2.3	6½	Survived	7.4	8.6	8.9	Do.

[1] First dose 100 mg. per kg., subsequent doses 200 mg. per kg.

dose of 2.0 gm. per kg., the animals usually died within 18 to 48 hours with characteristic pleural effusions, with a protein content of from 4.4 to over 6.6 percent. Plasma protein determinations at death gave values which appear to fall within the normal range.

The chronic toxicity experiments in rabbits detailed in table 6 indicate that under these conditions pleural effusion occurs infrequently, and that there is no definite or characteristic change in the plasma protein in the course of intoxication. That the effects of the compound are cumulative is indicated by the fact that the animals generally succumbed from the additive effects of the several doses, each of which was no more than about 20 percent of the MLD.

EXPERIMENTS IN CATS

Four series of experiments were made in cats with a view to determining the effects of continued exposure to doses varying from 10 to 50 mg. per kg. per day. Our observations on the acute toxicity of ANTU in cats are limited, but in three experiments a single dose of 100 mg. per kg. killed two of the three animals used. Both animals had copious pleural effusion and a small amount in the pericardium.

The data in table 7 indicate that 20 to 50 mg. per kg. of ANTU given daily incorporated in the ration of lean ground meat usually killed cats in from 2 to 23 doses. Pleural effusion was present in 2 of the 5 animals on 50 mg. per kg. and 3 of the 5 animals on 20 mg. per kg. The effusions had a protein content of from 2.4 to 4.3 per-

TABLE 7.—*Chronic toxicity of ANTU in cats at three different dose levels, oral administration*

Cat number	Weight (kg.)		Number of doses given	Died or survived	Remarks
	Initial	Final			
50 mg. per kg.:					
1	2.2	2.0	8	Died	
2	2.2	1.1	22	do	Terminal plasma bilirubin 2.9 mg. percent.
5	2.0		4	do	Pleural effusion protein 2.4 percent.
6	2.1		2	do	Pleural effusion protein 3.0 percent.
7	2.1	1.2	23	Survived	
20 mg. per kg:.					
3	2.3		2	Died	Pleural effusion protein 3.7 percent.
4	2.7		23	Survived	
8	2.5	2.0	23	Died	Terminal plasma bilirubin 25 mg. percent.
9	2.5	2.5	11	do	Pleural effusion protein 4.3 percent.
10	2.6	2.6	12	do	Pleural effusion protein 3.3 percent.
10 mg. per kg.:					
3	2.3	2.2	20	Died	Initial plasma protein 5.7 percent; terminal 6.9 percent.
4	3.2	2.8	30	Survived	Initial plasma protein 5.5 percent; terminal 4.4 percent.
5	2.3	2.4	30	do	Initial plasma protein 5.2 percent; terminal 4.4 percent.
7	2.1	2.2	30	do	Initial plasma protein 5.8 percent; terminal 4.5 percent.
8	2.4	2.2	27	do	Initial plasma protein 6.4 percent; terminal 6.2 percent.

cent. A dose of 10 mg. per kg. similarly given daily over a period of 36 days was usually survived. Plasma protein determinations in the series of five cats on 10 mg. per kg. per day at the beginning and at the end of the experiment indicate a reduction in the protein content with the progression of intoxication in three animals and no change in two. The determinations were made by the refractometric method (*4*) and the values are probably too low.

Hematologic studies in the course of this experiment which were essentially negative in other respects revealed the appearance of bilirubinemia in some of the animals. Accordingly, another experiment was set up with a view to studying this in greater detail. A series of seven animals had their plasma protein and plasma bilirubin determined before the drug was given and then again at weekly intervals during the course of chronic intoxication, which consisted of 20 mg. per kg. per day. Changes in the plasma protein values in the interim did not appear significant and only the initial and final values are given in table 8 which summarizes the results of this experiment.

TABLE 8.—*Chronic toxicity of ANTU in cats, oral administration, 20 mg. per kg. per dose until death*

Cat number	Weight (kg.)		Number of doses given	Days survived	Plasma protein (percent)		Bilirubin, mg. percent at—			
	Initial	Final			Initial	Final	0 days	14 days	21 days	25 days
11	3.1	2.6	10	20	7.1	8.0	0	2.9	------	------
12	2.6	2.2	12	25	6.5	5.9	0	trace	trace	8.9
13	1.8	1.8	19	24	7.1	5.9	0	0	1.3	------
14	3.4	3.0	15	21	6.9	7.2	0	0	2.3	------
15	2.5	2.0	4	22	7.2	6.5	0	0	4.0	------
16	2.9	2.4	11	23	6.7	7.0	0	3.5	20.8	------
17	2.3	1.(	22	28	5.8	5.4	0	0	2.6	7.3

The plasma bilirubin values determined by a method previously described (*6*) are shown in greater detail and indicate a consistent bilirubinemia, with an onset at from 14 to 21 days after the start of the experiment. The bilirubinemia is rapidly progressive in nature. Though its exact cause has not been established it appears to be hepatogenous in origin because of the direct van den Bergh reaction which could be elicited in every instance, and because of lack of consistent evidence of excessive blood destruction and anemia, except possibly in two animals in which the hemoglobin fell from 12.3 to 6.8 and from 14.0 to 9.3 gm. On the basis of this and the histopathological evidence described below it would appear most likely that the bilirubinemia may be the result of leakage of bile from the bile canaliculi into the venous sinusoids. Increased capillary permeability in this

situation appears to be the cause of the bilirubinemia, as the altered permeability in the pulmonary vascular bed would seem to be the cause of the pleural effusions.

It should be noted in this connection that Gargill and Lesses (*7*), who have recently reported on toxic reactions to thiouracil, describe jaundice in some of their cases which they believe was due to obstruction of the intrahepatic biliary tract. The icterus in their cases persisted for as long as 100 days.

SUMMARY

The acute and chronic toxicity of alphanaphthylthiourea (ANTU) was studied in albino rats, rabbits, cats, and dogs, with the following results:

1. The acute toxicity of ANTU varies in different animal species, rats and dogs being the most susceptible and rabbits the least.
2. Pleural, and to a lesser extent pericardial, effusions are characteristically present in all species if death is not delayed much beyond 24 hours.
3. The effusions have a protein content usually over one-half that of the plasma.
4. Tolerance to the acute toxicity of ANTU can be induced in rats by administering progressively increasing doses at 3- to 4-day intervals. No effusions have been found in tolerant rats dying from large doses.
5. Chronic toxicity experiments in rabbits and cats indicate a cumulative action.
6. In chronically poisoned cats effusions are absent, but instead bilirubinemia is regularly produced, and this seems to be the result of altered capillary permeability with leakage of bile from the bile channels into the venous sinusoids.

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II. PATHOLOGY[1]

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The material studied comprised 4 rabbits, dead on the seventh to twentieth day; 8 rats, dead at 14 to 34 days; and 17 cats, dying or killed at 13 to 38 days.

Because of an icterus of fairly marked grade observed in some of the cats, attention centered at first on the liver, and in the present series of

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

rats only that organ was saved for study. In this species there was a moderate to severe fatty degeneration in all 8 animals, perhaps more pronounced in the midzones of the lobules and least in the center. Fat droplets were usually fine and dispersed throughout liver-cell cytoplasm. Sometimes segregation in the borders of the cytoplasm was noted, and medium and coarse fat globules appeared infrequently. Hemosiderosis of scattered littoral cells was noted in one rat, while in five the ferrocyanide test revealed no iron. Only in one of the eight rats were there noted a few patches of cytoplasmic oxyphilia and slight karyorrhexis of centrolobular liver cells, perhaps with a few polymorphonuclear leucocytes.

In rabbits also there was constantly an irregular midzonal to diffuse fatty degeneration of liver cells. Fat droplets were generally small and dispersed throughout the cytoplasm, sometimes restricted to the cell-border zone. In one of the four animals there were vague areas of cytoplasmic oxyphilia and slight karyorrhexis of liver cells but no definite necrosis. In the rest bulky areas of coagulation necrosis were present, usually midzonal, sometimes diffuse. Periportal islets of surviving liver cells were more frequent than centrolobular. In some areas of necrosis capillary thrombosis was noted; in some, polymorphonuclear leucocyte infiltration; and in others, proliferation of stroma cells, depletion of liver cells, and formation of wide blood spaces. In one rabbit a partial interportal trabeculation by strands of delicate collagen fibrils was noted, while in three the bulky portal scars and lymphocyte infiltrations often seen in rabbits were absent.

As in rats and rabbits the liver of the cat almost regularly presented a moderate to severe fatty degeneration. In individual liver cells fat droplets were usually fine or medium in size and dispersed throughout the cytoplasm. Involvement was usually greatest in the midzones of the lobules, sometimes least, sometimes most in the centers of the lobules.

In 10 of the 17 cats there was moderate to pronounced centrolobular congestion, accompanied in 4 by atrophy of cell cords and in 2 of these by centrolobular cytoplasmic oxyphilia grading into coagulation necrosis.

Icterus was grossly evident in nine cats. These cats gave maximum serum bilirubin levels at or before death varying from 1.3 to 20.8 mg. per 100 cc. Several showed green discoloration of the urine in the bladder. In two or three, green zones were seen across the base of the renal pyramids on section. In five of these cats the bile capillaries throughout the liver lobule were distended by threads of apparently inspissated bile. Larger bile ducts in these cats sometimes contained hyaline oxyphilic masses, mucus, or mucopurulent exudate. However, the gall bladders were regularly distended with dark-green,

thick, viscid bile, and the intestinal contents were always bile-stained. Small bile ducts were often normal.

However, in the 20 mg. per kg. series, seven of eight cats surviving 19 days or more presented in the periportal areas and often along the interportal lines more or less numerous solid cords and narrow tubules of small basophilic epithelial cells. Mitoses were sometimes seen in these cells.

Often more or less swelling of phagocytic littoral cells was noted, and in 11 of the 17 cats these cells contained considerable amounts of demonstrable ferric iron, either as diffuse cytoplasmic staining or as granular light-brown pigment. In a few cats, brown iron-free pigment was present as well as typical hemosiderin.

The gall bladder was normal, though partly autolyzed in six cats, while in the seventh there was much irregular infiltration of the mucosa by lymphocytes and fewer macrophages with ingested nuclear fragments.

The pancreas in one rabbit contained areas of necrosis of lobules, grading from purulent infiltration and coagulated necrotic acini peripherally to caseation centrally. In another rabbit the pancreas was normal. Usually the pancreas was normal in cats but in cat 16, in which the most pronounced small bile duct proliferation was seen, there were also many proliferating small tubules of basophilic cells about the large pancreatic duct adjacent to the duodenum.

In rabbits, splenic follicles were variously composed chiefly of small lymphocytes or a mixture of small and large lymphoid cells. Only in the animal killed at 7 days were there slight intrafollicular phagocytosis of nuclear debris, dilated and congested pulp sinuses, and an absence of demonstrable hemosiderin. All showed more or less swelling of sinus and pulp littoral cells, with or without numbers of macrophages in the sinuses. Erythrophagia was only infrequently demonstrable, but the three animals surviving 13 to 20 days presented more or less diffuse and granular iron-positive pigmentation of littoral cells and macrophages in the pulp. Lymphoid elements in the pulp were inconspicuous.

In cats, splenic pulp generally contained a moderate amount of blood and few to moderately numerous lymphocytes. Normoblasts were infrequently identifiable and megakaryocytes were rare. Slight to moderate hemosiderosis was present in 7 of 16 spleens, erythrophagia in 1. Hemosiderosis was noted in both livers and spleen in 6 cats, and in one or the other in 13 of the 17.

No consistent significant alterations were observed in 20 lymph nodes from 10 cats: 6 cervical, 7 thoracic, 7 abdominal. A cervical lymph node from 1 rabbit was likewise negative.

Thymus was normal in one cat.

Bone marrow of the sternum was studied in a single cat. It was

quite cellular, with a predominance of young forms, and active erythropoiesis as well as myelopoiesis.

Submaxillary gland from one rabbit was normal.

Esophagus was normal in the 4 rabbits and in 12 levels from 7 cats. In 1 cat the mucosa presented focal perivascular lymphocyte infiltration.

The trachea showed focal lymphocyte infiltration of the mucosa in most of the rabbits and cats. In one cat sections of adults and eggs of *Eucoleus serophilus* were identified in the mucosa.

In the thyroid in rabbits colloid was generally poorly stained, lightly oxyphil, perhaps granular or vacuolated in appearance. In two of the four animals moderate numbers of acini contained no stainable colloid, and others contained some moderately dense normal appearing colloid. In one of these, hyaline deeply basophil masses were present in a few acini. Acinar epithelium was generally cuboidal, sometimes low columnar. Interstitial congestion was sometimes present.

In three cats thyroid colloid was moderately oxyphilic and acini were of small to medium size. In the remaining five, colloid was very poorly stained in some areas, moderately oxyphil in others, sometimes granular, reticulated or vacuolated in appearance, and sometimes absent. Acini were more variable in size and in one cat there were lymphoid follicles and interstitial lymphocyte infiltration.

Single parathyroids were normal in each of 3 rabbits, and 11 normal parathyroids were found in 6 cats.

Small intestine was normal in three cats, in one a catarrhal enteritis was present, in two there were scattered pus-filled glands, and in one an area of hemorrhagic necrosis and ulceration with subjacent granulation was present. Stomach was normal in one cat, colon presented a catarrhal reaction in another, and buccal mucosa showed focal lymphocyte infiltration in a third. Areas of omental necrosis or suppuration were noted in two of seven cats.

In one rabbit killed after 7 days there was extensive serous exudate alternating with and grading into hemorrhage in the pulmonary alveoli. In another there were no histologic lesions of the lung, and no material was saved from the other two.

In the lungs of the cats receiving 10 mg. per kg. dosage only slight and apparently nonspecific changes were noted. Catarrhal bronchitis in moderate grade was seen in 5 of 10 cats on 20 mg. per kg. dosage, in 6 there was slight to marked serous to serosanguinous exudation in alveoli, with some macrophages and epithelial cells in the exudate in some. In 4 of these cats proliferative changes were noted. In 1 these were localized in 1 of 4 sections and consisted of peribronchial epithelialization of alveoli accompanying a purulent bronchitis. In 3 others there was thickened deeply basophil atriobronchiolar epithelium, sometimes with slight stratification and

irregular arrangement of nuclei. These proliferative changes were found only in the presence of serous, serosanguinous, and serocellular exudates.

In several cats treated for 25 to 38 days there was more or less copious mucoid material in the media of the aorta or pulmonary artery near the base of the heart. Other animals treated 25 days or less did not show this picture.

In 10 of 15 cats few to numerous heart muscle fibers contained few to numerous fine fat droplets. Cross striation was usually plainly evident. Focal lesions were few and inconstant, but included a few necrotic muscle fibers in 2 cats, focal hemorrhage in 2, focal scarring or fibroblast reaction in 4, focal polymorphonuclear infiltration in 2. In 8 cats there were no focal lesions.

Skeletal muscle was normal in six cats; contained few and numerous sarcosporidia respectively in two more, and in one there were some hyaline oxyphilic muscle fibers and some interstitial and fascial mucoid exudate. In one rabbit, also, skeletal muscle was normal.

In one rabbit the adrenal was normal, and its cortex moderately heavily laden with fatty substances. In cats lipid content of the cortex seemed diminished, and fine fat droplets were most often concentrated in the outer half of the fascicular zone. The medulla was normally composed largely of chromaffin cells in five cats. In the two remaining cats the chromaffin tissue was partly replaced by solid areas of larger, more basophilic, chromaffin-free cells. Abutting directly on the large-cell areas were strands or solid areas of smaller cells containing much chromaffin.

In all four rabbits, fatty changes were observed in the renal epithelium. Usually moderately severe accumulation of fine fat droplets was seen in loop tubules in the corticomedullary border. Both droplet size and frequency were more variable in the epithelium of the convoluted tubules, varying from few fine droplets to numerous fine and medium fat globules. In one rabbit glomerular epithelium participated in the fatty alteration. Desquamation of fatty cells was noted in another rabbit, and interstitial fat phagocytes were also seen in this animal. In addition this rabbit presented calcification of scattered cortical tubules, hyaline glomerular thrombi, and many hyaline casts. Pelvic and cortical lymphocyte infiltration was seen in one rabbit, cortical infiltration alone in another.

In 4 of 15 cats there were found more or less numerous bile casts, chiefly in the large collecting tubules in the basal half of the renal pyramid, fewer in cortical convoluted tubules. Otherwise the kidney presented the usual normal heavy fatty infiltration of the epithelium of convoluted and often loop tubules, and scattered foci of lymphocyte infiltration in cortex and in pelvic mucosa which are probably assignable to intercurrent natural infections.

SUMMARY

Alphanaphthylthiourea produces a fatty degeneration of the liver of fine-droplet type in rats, rabbits, and cats. Necrosis was inconspicuous in rats and cats, and prominent in rabbits. In cats there is often further an intrahepatic obstructive icterus with bile casts in the kidneys as well as in the hepatic bile capillaries and in some animals there appears a prominent proliferation of small bile ducts.

Often there is a moderate splenic and hepatic hemosiderosis in cats, and splenic hemosiderosis in rabbits. A moderate thyroid hyperactivity is noted, more pronounced in rabbits than in cats.

Pulmonary edema and hemorrhage were noted in rabbits and cats in addition to the grossly observed hydrothorax in all three species. In the cats there was sometimes a conspicuous atriobronchiolar epithelial hyperplasia.

There were conspicuous fatty changes in the renal epithelium in rabbits, but it is not possible to state whether the normal fatty condition of the renal cortex in cats was exaggerated.

In the adrenal medulla of the cat, hyperplastic changes were noted.

A NOTE ON PHYSICIAN TIME PER PATIENT IN PRIVATE PRACTICE

By Burnet M. Davis, *Surgeon (R), United States Public Health Service* [1]

INTRODUCTION

A basic problem in estimating the number of physicians required to satisfy the demands of a population for medical care is the determination of the amount of physician time required per office visit. Because of the individualistic nature of medical practice, such determinations are difficult to make, particularly in respect to physicians engaged in private office practice.

Some years ago Lee and Jones (*1*) postulated, on the basis of a number of expert opinions, the amount of physician time required for proper diagnosis and treatment of specific categories of disease. It is of some interest that these authors used 15 minutes per general practitioner office visit as a reasonable time for handling routine types of cases.

On the other hand, Ciocco and Altman (*2*) have presented data from which the average length of time per office visit of private general practitioners in Maryland in 1942 may be estimated at 20.6 minutes.[2] This estimate includes an unknown amount of time spent in the office

[1] From the Division of Public Health Methods. Grateful acknowlegement is made to Assistant Statistician Marion E. Altenderfer for her assistance in handling the statistical material presented.

[2] Computed from data in tables 4 and 9, *op. cit.*, on the assumption of a 5½-day week.

while not actually seeing patients, but, unlike that of Lee and Jones, represents actually prevailing practice in the area studied.

The present report describes the findings of a study of the time spent and the number of patients seen by six individual physicians engaged in private practice in a war industrial area in 1944.

METHOD OF STUDY

During December 1943 six physicians in a war-swollen community were induced by a local housing authority to hold office hours on a rotating schedule in two war-housing projects. An understanding was worked out between the housing authority, representatives of the local medical society, and the individual physicians concerned. The housing authority agreed to make office space available (one office in each of two projects) and in cooperation with local voluntary agencies, to provide nursing and clerical assistance.

The physicians agreed that at specified times on each week day, namely, 10:30 a. m., 4:30 p. m., and 7:30 p. m., a physician would be present at one office or the other, or both. A weekly schedule, stating the name of the physician to be present at each period, was worked out and posted in the projects. The number of periods per week scheduled for each physician varied considerably, depending on the amount of time each felt able to give to practice in the war-housing projects (table 1, column 2). On the average, approximately 27 out of the possible 36 periods per week were scheduled by the 6 physicians in the 13 weeks studied.

It was agreed that the physician would not be expected to remain for any specified length of time, but could leave as soon as all patients present had been seen. To be sure of seeing the physician, therefore, patients had to arrive at or soon after the scheduled time. This procedure resulted in much waiting time by the patients but reduced waste time on the physician's part to a minimum.

All of the physicians had been previously practicing in the area and each of them continued to maintain his private office in the prewar areas of the community. All physician-patient relationships, both professional and financial, were on a strictly private practice basis, the physician making his own arrangements with regard to collection of fees. It is to be emphasized that this was not a group practice scheme; the individual physicians collaborated in working out the weekly schedule, but only one physician was present in the office at any one period, and each carried on a general practice.

Records were kept by the nursing and clerical staff of the time of arrival and departure of each physician and the number of patients seen at each period. Despite other heavy demands on the physicians' time, the experience during the 3 months studied revealed that the

physicians lived up to the posted schedule with commendable conscientiousness and only in rare instances were patients left without a physician at a scheduled period.

FINDINGS

During the months of January, February, and March 1944, 357 periods were scheduled and in all but 7 instances the physician was present. Data for analysis were available for 318 of these periods, since for 17 the time of arrival or of departure was not recorded and at 15 additional periods no patients presented themselves.

Variation among physicians.—The 318 periods were distributed among the 6 physicians as shown in table 1. The physicians are listed in order of decreasing number of periods attended; it will be noted that

TABLE 1.—*Patient load and physician time per patient, by individual physician*

(1)	(2)	(3)	(4)	(5)	(6)
Physician	Number of periods	Number of patients	Average number of patients per period	Average minutes per patient	
				All periods	Excluding single-patient periods [1]
All physicians	318	1,602	5.0	17.3	16.9
A	91	395	4.3	12.7	12.2
B	74	505	6.8	19.2	19.2
C	63	317	5.0	17.3	17.0
D	39	149	3.8	20.2	18.8
E	36	163	4.5	17.7	17.6
F	15	73	4.9	21.6	21.3

[1] The number of periods at which only 1 patient was seen totaled 27, as follows: Drs. A, 13; B, 3; C, 3; D, 5; E, 1; F, 2.

there is considerable variation in the average number of patients seen per period by the several physicians. It is reasonable to consider column (2) as indicating the amount of service the physician was willing to offer, and column (4) as a rough index of the physician's popularity.

Column (5) shows the average time per patient for each of the physicians. Since it was generally understood that the physician would leave as soon as the patients waiting in the office had been seen, it seems unlikely that these figures include an appreciable amount of time spent by the physician in waiting. A possible exception exists in the 27 periods at which only a single patient was seen, since the physician might wait a few minutes if no patients were present at the time of his arrival. However, he was very unlikely to wait further after seeing one or more patients.

Column (6) shows the average time per patient for the 291 periods at which 2 or more patients were seen; it is believed that these figures more truly represent the amount of time actually spent seeing patients.

It is evident that there is considerable variation in the average amount of time devoted to each patient by the several physicians. Reference to column (4), shows that the speed of seeing patients is not directly related to the average number of patients seen by the respective physicians. For example, Dr. A saw on the average only two-thirds as many patients per period as did Dr. B, yet Dr. B spent more than half again as much time per patient as did Dr. A. The differences found in average time per patient appear to be the result of individual differences in habits of practice.

Time per patient in different periods.—Taking the data for all 6 physicians together, examination of the average time per patient for each of the 318 periods (and for the 291 periods remaining when single-patient periods are excluded) shows the distribution presented in table 2.

TABLE 2.—*Distribution of periods by physician time per patient*

Average minutes per patient	Number of periods		
	Total	Single patient	Excluding single-patient periods
Total	318	27	291
Less than 10.0	25	0	25
10.0–14.9	73	2	71
15.0–19.9	91	2	89
20.0–24.9	61	1	60
25.0–29.9	22	2	20
30.0–34.9	23	10	13
35.0 and over	23	10	13

The extent of the range (the extremes were 5.0 and 100 minutes, or 5.0 and 45 minutes excluding single-patient periods) is of some interest. As would be expected from the average of 16.9 minutes (table 1) the largest number of periods shows a per-patient time of between 15 and 20 minutes. In more than half of the periods (52 percent of total; 55 percent excluding single-patient periods) the average time spent per patient ranged between 10 and 20 minutes. It will be noted that the number of single-patient periods is greatest for the two longest time intervals.

Under the prevailing arrangement without an appointment system, the number of patients seen per period varied widely, from no patients (15 periods) to a maximum of 16 patients (2 periods). Table 3 shows this distribution: the most frequent number of patients seen was 5, but 3- and 6-patient periods occurred nearly as often.

Table 3 also shows the average physician time per patient for each group of periods at which the specified numbers of patients were seen. It is evident that there is a steady decrease in the time per patient as the number of patients per period increases. The findings suggest

TABLE 3.—*(a) Distribution of periods by number of patients seen; and (b) variation in average physician time per patient with number of patients per period*

Number of patients seen in period	Number of periods	Average physician time per patient (minutes)	Number of patients seen in period	Number of periods	Average physician time per patient (minutes)
All periods	318	17.3	5	49	16.4
			6	45	16.2
1	27	36.5	7	21	16.3
2	35	25.1	8	17	15.8
3	47	20.7	9	20	14.4
4	36	17.6	10 or more	21	15.0

that a minimum time of around 15 minutes per patient tends to be reached. As suggested above in connection with table 1, the time recorded for single-patient periods possibly includes some waiting time, so that the figure of 36.5 minutes shown for this group may be somewhat high. But even if this group of periods is excluded, as has been done in figure 1, the phenomenon is striking.

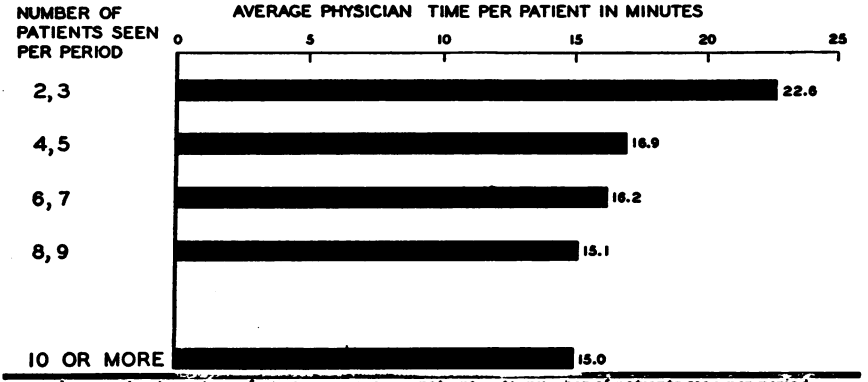

FIGURE 1.—Variation of physician time per patient with number of patients seen per period.

To permit use of averages based on larger numbers of periods, the groups have been combined in pairs in figure 1, in addition to excluding the 1-patient periods. Thus, the 5 bars are based on averages of 82, 85, 66, 37, and 21 periods at which 209, 389, 417, 316, and 244 patients, respectively, were seen.

DISCUSSION

It is recognized that the conditions under which this study was done are not, in all respects, typical of private medical practice. However, there would seem to be no reason why the conditions prevailing so far as the professional work is concerned should be significantly different from that in ordinary private practice by busy physicians in wartime. The physicians had the full-time services of a nurse and the usual amount of basic office equipment with which to work. It is believed that the type of practice involved was generally similar to that carried on by general practitioners in medium-sized cities.

The over-all average of approximately 17 minutes per patient is quite close to Ciocco and Altman's findings in Maryland (20.6 minutes), when allowance is made for some waiting time in the latter figure, and for the probability that the physicians in this war-swollen community were under greater pressure than the average Maryland physician in 1942.

It is of interest to note the extent of variation among the physicians in average time per patient. While too few physicians were involved to warrant analysis of the differences observed, it may be seen that even in this small group four physicians spent on the average more than half again as much time per patient as did the physician whose average time was lowest.

The relationship shown in figure 1 between the time spent per patient and the number of patients merits further discussion. In general, nearly all of the patients arrived at approximately the time for which the period was scheduled and awaited their turns. It seems probable, therefore, that the physician was generally aware of the number of patients waiting to see him and tended to adjust the speed of his work accordingly. It is difficult to see how the observed phenomenon can be explained otherwise since the variation is too consistent and based on too large a number of observations to be the result of chance. If this is the correct interpretation, this would seem to be rather strong evidence in favor of an organized appointment system to distribute the patient load as evenly as possible.

If physicians require more than 20 minutes per patient to diagnose and treat those who happen to present themselves 2 or 3 at a time, can patients who arrive 8 or 10 at a time expect adequate study and treatment in 15 minutes each? Under any organized method of provision of medical care, no less than in private practice, it would seem essential to safeguard the physician from undue pressure to dispose of patients more rapidly than is consistent with a high quality of professional work.

SUMMARY

Data are presented on time spent by 6 private general practitioners in holding 318 office periods comprising 1,602 patient visits in the first 3 months of 1944. The main findings were:

1. The average time spent per patient was 16.9 minutes but varied among the six physicians from 12.2 to 21.3 minutes.

2. The average time per patient decreased steadily as the number of patients per office period increased.

REFERENCES

(1) Lee, R. I., and Jones, L. W.: The Fundamentals of Good Medical Care. Publication No. 22 of the Committee on the Costs of Medical Care. Chicago, 1933. University of Chicago Press.
(2) Ciocco, A., and Altman, I.: Statistics on the patient load of physicians in private practice. J. Am. Med. Assoc., 121: 506–513 (1943).

DEATHS DURING WEEK ENDED AUGUST 25, 1945

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

	Week ended Aug. 25, 1945	Corresponding week, 1944
Data for 93 large cities of the United States:		
Total deaths	8,557	7,472
Average for 3 prior years	7,602	
Total deaths, first 34 weeks of year	308,436	312,399
Deaths, under 1 year of age	617	601
Average for 3 prior years	623	
Deaths under 1 year of age, first 34 weeks of year	20,573	21,073
Data from industrial insurance companies:		
Policies in force	67,376,258	66,705,582
Number of death claims	12,865	12,097
Death claims per 1,000 policies in force, annual rate	10.0	9.5
Death claims per 1,000 policies, first 34 weeks of year, annual rate	10.4	10.2

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

REPORTS FROM STATES FOR WEEK ENDED SEPTEMBER 1, 1945

Summary

The current week is the first week since July 7 during which the total reported cases of poliomyelitis declined—917 cases were reported currently, as compared with 931 for the preceding week and 1,682 for the corresponding week in 1944, which was the peak for that year. If recorded by date of onset instead of by date of reports received by the local health officers, the peak of incidence would probably be a week or 10 days earlier. Currently, the largest numerical decreases occurred in New York (from 191 to 138), Illinois (from 121 to 94), and Texas (from 73 to 33), while the largest increases were reported in Missouri (8 to 29), Utah (14 to 34), (Iowa 19 to 31), New Jersey (88 to 96), Kansas (3 to 15), and Virginia (20 to 32). A total of 6,156 cases has been reported to date, as compared with 9,474 in 1944 and 5,886 in 1943 for the same period.

In addition to poliomyelitis, the incidence to date of diphtheria, meningococcus meningitis, scarlet fever, and endemic typhus fever is above the normal expectancy, and there is some indication of an increase in the death rate for diphtheria during the first half of 1945. Incidence below the median expectancy has been recorded to date for influenza, measles, smallpox, typhoid fever, and whooping cough—measles less than one-fifth the incidence in 1943 and 1944, and both smallpox and typhoid fever below the respective figures for any prior year. A total of 22 cases of anthrax has been reported to date, as compared with 31 cases for the corresponding period in 1944.

Although reports from 93 large cities in the United States for the past two weeks show a higher urban mortality than for the same weeks last year, the total to date is below that for last year. Currently 8,548 deaths were recorded in these cities, as compared with 8,557 for the preceding week, 7,610 for the same week in 1944, and a three-year average of 7,747. To date this year a total of 316,984 deaths has been reported, as compared with 320,009 for the same period last year.

Telegraphic morbidity reports from State health officers for the week ended September 1, 1945, and comparison with corresponding week of 1944 and 5-year median

In these tables a zero indicates a definite report, while leaders imply that, although none was reported, cases may have occurred.

Division and State	Diphtheria			Influenza			Measles			Meningitis, meningococcus		
	Week ended—		Median 1940–44	Week ended—		Median 1940–44	Week ended—		Median 1940–44	Week ended—		Median 1940–44
	Sept. 1, 1945	Sept. 2, 1944		Sept. 1, 1945	Sept. 2, 1944		Sept. 1, 1945	Sept. 2, 1944		Sept. 1, 1945	Sept. 2, 1944	
NEW ENGLAND												
Maine	0	0	0	-------	-------	-------	1	9	11	0	0	0
New Hampshire	0	0	0	-------	-------	-------	0	0	0	0	1	0
Vermont	0	0	0	-------	-------	-------	14	2	2	0	0	0
Massachusetts	3	4	1	-------	-------	-------	46	26	38	0	4	2
Rhode Island	0	2	0	-------	-------	-------	0	1	3	0	1	0
Connecticut	0	1	0	-------	2	1	11	11	11	3	5	0
MIDDLE ATLANTIC												
New York	13	6	6	[1] 2	[1] 1	[1] 2	24	50	57	2	19	8
New Jersey	2	0	2	-------	1	2	12	12	20	3	8	1
Pennsylvania	10	8	4	3	-------	-------	27	21	30	12	11	3
EAST NORTH CENTRAL												
Ohio	4	2	3	-------	5	5	7	8	24	2	8	1
Indiana	4	8	8	3	-------	4	2	2	1	1	0	1
Illinois	1	4	5	1	1	2	128	7	10	3	6	3
Michigan [2]	7	5	6	-------	1	1	24	4	16	5	9	2
Wisconsin	3	2	1	13	2	11	17	113	79	1	2	1
WEST NORTH CENTRAL												
Minnesota	7	0	2	-------	-------	-------	2	3	3	1	1	1
Iowa	3	2	2	-------	-------	-------	0	3	4	0	0	0
Missouri	2	1	1	2	-------	-------	3	4	4	0	5	3
North Dakota	0	3	1	8	5	5	1	3	3	0	3	0
South Dakota	3	2	2	-------	-------	-------	2	0	3	0	0	0
Nebraska	0	2	1	1	-------	-------	1	1	2	0	1	0
Kansas	8	5	3	-------	-------	-------	13	4	8	1	0	0
SOUTH ATLANTIC												
Delaware	0	0	0	-------	-------	-------	3	0	0	0	1	0
Maryland [2]	6	5	1	-------	-------	2	3	9	9	0	0	1
District of Columbia	0	0	0	-------	-------	-------	0	1	3	0	0	0
Virginia	5	6	5	83	24	30	4	5	5	0	1	1
West Virginia	8	2	2	-------	1	1	0	2	2	1	1	2
North Carolina	34	3	27	-------	5	-------	4	12	10	1	5	2
South Carolina	10	11	10	143	64	64	4	5	5	2	0	1
Georgia	9	12	12	2	52	19	1	13	7	0	0	0
Florida	6	7	3	2	1	3	1	72	4	2	2	0
EAST SOUTH CENTRAL												
Kentucky	7	9	7	-------	1	2	4	2	8	1	5	1
Tennessee	8	5	5	5	6	4	5	1	3	2	1	1
Alabama	18	6	9	1	12	12	0	3	16	1	2	2
Mississippi [2]	13	10	11	-------	-------	-------	-------	-------	-------	0	1	0
WEST SOUTH CENTRAL												
Arkansas	11	4	6	47	10	2	7	6	6	2	1	0
Louisiana	4	4	2	5	-------	1	1	0	0	0	1	1
Oklahoma	5	5	5	3	7	6	5	10	2	0	0	0
Texas	41	15	20	285	216	216	22	28	29	4	2	2
MOUNTAIN												
Montana	2	15	2	3	-------	-------	24	0	9	0	0	0
Idaho	3	0	0	6	-------	-------	20	0	1	0	0	0
Wyoming	0	0	0	-------	-------	-------	1	0	0	0	0	0
Colorado	1	4	4	4	27	11	5	0	14	2	0	0
New Mexico	2	5	1	2	-------	-------	2	2	4	0	0	0
Arizona	2	0	0	12	12	30	0	2	4	0	0	0
Utah [2]	0	0	0	-------	-------	1	43	7	7	0	0	0
Nevada	0	0	0	-------	1	-------	0	4	0	0	0	0
PACIFIC												
Washington	2	5	2	-------	1	-------	30	32	17	2	3	1
Oregon	2	0	1	3	5	4	9	18	16	1	1	1
California	15	15	10	10	28	16	129	150	62	4	12	2
Total	284	205	205	649	491	491	662	668	668	59	123	41
35 weeks	8,894	7,212	7,871	72,310	339,669	169,989	102,559	592,322	539,146	6,326	13,371	2,495

[1] New York City only.

[2] Period ended earlier than Saturday.

Telegraphic morbidity reports from State health officers for the week ended September 1, 1945, and comparison with corresponding week of 1944 and 5-year median—Con.

Division and State	Poliomyelitis			Scarlet fever			Smallpox			Typhoid and paratyphoid fever [2]		
	Week ended—		Median 1940–44	Week ended—		Median 1940–44	Week ended—		Median 1940–44	Week ended—		Median 1940–44
	Sept. 1, 1945	Sept. 2, 1944		Sept. 1, 1945	Sept. 2, 1944		Sept. 1, 1945	Sept. 2, 1944		Sept. 1, 1945	Sept. 2, 1944	
NEW ENGLAND												
Maine	3	1	1	5	10	3	0	0	0	1	0	1
New Hampshire	3	11	1	9	0	2	0	0	0	0	0	0
Vermont	5	7	0	0	0	1	0	0	0	0	1	0
Massachusetts	32	35	20	29	32	47	0	0	0	38	2	3
Rhode Island	0	1	1	2	2	3	0	0	0	2	1	0
Connecticut	20	20	6	7	10	8	0	0	0	2	2	2
MIDDLE ATLANTIC												
New York	138	666	58	73	56	56	0	0	0	10	16	13
New Jersey	96	67	21	18	15	19	0	0	0	5	3	4
Pennsylvania	61	162	13	41	34	41	0	0	0	11	3	18
EAST NORTH CENTRAL												
Ohio	33	105	21	44	50	50	1	0	0	6	13	13
Indiana	22	27	7	11	11	11	0	0	0	3	4	4
Illinois	94	37	36	37	18	43	0	0	0	2	3	10
Michigan [1]	13	120	26	32	26	31	0	0	0	3	2	6
Wisconsin	15	32	18	47	27	30	0	0	0	0	2	1
WEST NORTH CENTRAL												
Minnesota	9	40	11	15	11	15	0	0	0	0	0	0
Iowa	31	7	7	5	6	13	0	0	0	2	1	1
Missouri	29	11	11	14	11	11	0	0	0	4	11	9
North Dakota	0	4	1	10	2	2	1	0	0	0	1	0
South Dakota	4	0	1	2	0	9	0	0	0	1	1	0
Nebraska	9	7	7	2	7	3	0	0	0	0	0	0
Kansas	15	8	8	30	23	20	0	0	0	1	5	5
SOUTH ATLANTIC												
Delaware	4	4	0	2	2	2	0	0	0	1	0	0
Maryland [1]	3	47	2	9	14	9	0	0	0	2	2	2
District of Columbia	8	22	0	0	2	4	0	0	0	1	0	1
Virginia	32	65	5	17	11	7	0	0	0	3	5	5
West Virginia	1	14	6	23	36	21	0	0	0	8	4	6
North Carolina	10	41	3	38	27	23	0	0	0	1	7	9
South Carolina	12	4	1	6	2	4	0	0	0	6	2	4
Georgia	6	8	3	7	6	6	1	2	0	7	6	8
Florida	4	2	2	3	1	2	0	0	0	2	2	3
EAST SOUTH CENTRAL												
Kentucky	2	34	10	22	13	17	0	0	0	7	7	15
Tennessee	23	5	4	29	9	10	0	0	0	12	1	15
Alabama	2	2	3	7	6	20	0	0	0	3	1	6
Mississippi [1]	3	7	3	8	7	6	0	0	0	1	3	11
WEST SOUTH CENTRAL												
Arkansas	4	3	3	0	3	3	0	0	0	2	9	9
Louisiana	7	1	1	1	1	2	0	0	0	3	1	7
Oklahoma	16	2	2	4	3	5	0	0	0	2	3	6
Texas	33	8	8	43	20	17	0	0	0	17	17	17
MOUNTAIN												
Montana	0	0	3	6	4	8	0	0	0	4	0	1
Idaho	3	1	1	3	3	3	0	0	0	1	0	0
Wyoming	2	0	0	3	0	1	0	0	0	0	0	0
Colorado	15	5	3	10	10	10	0	0	0	4	0	0
New Mexico	0	1	1	2	3	3	0	0	0	3	2	2
Arizona	1	1	1	2	1	1	0	0	0	3	3	3
Utah [1]	34	2	3	0	4	2	0	0	0	0	0	0
Nevada	0	2	0	0	0	0	0	0	0	0	0	0
PACIFIC												
Washington	22	12	12	15	21	9	0	0	0	2	0	3
Oregon	5	11	5	8	7	7	0	0	0	0	2	1
California	*33	10	12	81	87	39	0	0	0	7	1	2
Total	917	1,682	620	782	654	654	3	2	7	193	149	231
35 weeks	*6,156	9,474	4,026	136,195	148,893	99,317	273	307	621	3,111	3,596	4,498

[1] Period ended earlier than Saturday.

[2] Including paratyphoid fever reported separately, as follows: Massachusetts 37; Rhode Island 2; Connecticut 1; New Jersey 2; South Carolina 3; Georgia 1; Texas 2; Colorado 2; New Mexico 1; California 3.

*Correction: California, week ended Aug. 11, poliomyelitis 40 (instead of 10).

Telegraphic morbidity reports from State health officers for the week ended September 1, 1945, and comparison with corresponding week of 1944 and 5-year median—Con.

Division and State	Whooping cough			Week ended Sept. 1, 1945							
	Week ended—		Median 1940–44	Dysentery			Encephalitis, infectious	Rocky Mt. spotted fever	Tularemia	Typhus fever, endemic	Undulant fever
	Sept. 1, 1945	Sept. 2, 1944		Amebic	Bacillary	Unspecified					
NEW ENGLAND											
Maine	16	20	20	0	0	0	0	0	0	0	0
New Hampshire	2	0	0	0	0	0	0	0	0	0	1
Vermont	14	9	16	0	0	0	0	0	0	0	3
Massachusetts	131	69	72	0	39	0	0	0	0	0	0
Rhode Island	18	6	6	0	3	0	0	0	0	0	0
Connecticut	45	30	30	1	1	0	1	0	0	0	2
MIDDLE ATLANTIC											
New York	293	183	258	6	16	0	1	2	0	0	8
New Jersey	138	61	88	0	1	0	0	0	0	0	1
Pennsylvania	135	79	180	0	0	0	0	1	0	0	3
EAST NORTH CENTRAL											
Ohio	141	119	144	0	2	0	0	0	0	0	1
Indiana	9	2	19	1	0	0	1	0	0	0	0
Illinois	70	68	156	5	0	0	2	1	0	0	8
Michigan [3]	142	61	221	2	0	0	0	1	0	0	1
Wisconsin	51	120	208	0	0	0	0	0	0	0	3
WEST NORTH CENTRAL											
Minnesota	7	41	41	2	0	0	0	0	0	0	2
Iowa	10	10	23	5	0	0	0	0	0	0	2
Missouri	17	16	8	0	0	2	0	2	1	0	0
North Dakota	4	39	13	0	0	0	0	0	0	0	0
South Dakota	6	4	4	0	0	0	0	0	0	0	0
Nebraska	2	3	3	0	0	0	0	0	0	0	0
Kansas	50	38	38	1	0	0	1	0	1	0	1
SOUTH ATLANTIC											
Delaware	1	0	3	0	0	0	0	0	0	0	0
Maryland [3]	45	46	56	0	0	0	0	0	0	0	0
District of Columbia	8	0	10	0	0	0	0	0	0	0	0
Virginia	23	23	23	0	0	295	0	1	2	0	0
West Virginia	23	12	17	0	0	0	0	0	0	0	0
North Carolina	147	95	95	1	0	0	0	2	1	4	0
South Carolina	62	70	58	2	24	0	0	0	0	16	0
Georgia	21	2	13	1	5	3	0	0	1	37	5
Florida	3	19	19	1	0	0	0	0	0	14	1
EAST SOUTH CENTRAL											
Kentucky	36	34	34	0	0	0	0	0	0	0	0
Tennessee	28	15	27	0	0	3	0	1	2	1	2
Alabama	3	6	18	0	0	0	0	0	0	19	3
Mississippi [3]	----	----	----	0	0	0	0	0	1	5	1
WEST SOUTH CENTRAL											
Arkansas	10	8	8	0	14	0	0	0	2	0	1
Louisiana	1	1	1	2	0	0	0	0	0	9	3
Oklahoma	20	7	7	1	9	0	0	4	0	0	2
Texas	125	170	142	12	423	4	0	0	0	45	10
MOUNTAIN											
Montana	2	21	17	0	0	0	0	0	0	0	0
Idaho	1	1	1	0	7	0	0	0	0	0	0
Wyoming	5	1	2	0	0	0	0	0	0	0	0
Colorado	33	34	32	0	0	0	0	0	0	0	0
New Mexico	9	0	7	0	13	7	0	0	0	0	0
Arizona	4	26	13	0	0	26	0	0	0	0	0
Utah [3]	35	24	36	0	0	0	0	0	1	0	2
Nevada	0	0	0	0	0	0	0	0	0	0	0
PACIFIC											
Washington	36	19	36	0	0	0	0	0	0	0	1
Oregon	12	4	19	0	0	0	0	0	0	0	1
California	130	74	135	2	6	0	29	0	0	0	4
Total	2,124	1,690	2,536	45	563	340	35	14	13	150	72
Same week, 1944	1,690	----	----	39	617	218	41	8	11	157	52
Average, 1942–44	2,373	----	----	34	427	210	29	[4] 10	8	[4] 126	----
35 weeks: 1945	88,869	----	----	1,274	17,223	6,983	337	386	539	3,049	3,253
1944	66,648	----	----	1,179	15,160	5,640	442	389	397	3,091	2,459
Average, 1942–44	110,707	----	[4] 128,043	1,129	10,772	5,190	426	[4] 389	563	[4] 2,098	----

[3] Period ended earlier than Saturday.
[4] 5-year median, 1940–44.

Leprosy: New Jersey 1 case.

WEEKLY REPORTS FROM CITIES

City reports for week ended August 25, 1945

This table lists the reports from 84 cities of more than 10,000 population distributed throughout the United States, and represents a cross section of the current urban incidence of the diseases included in the table.

	Diphtheria cases	Encephalitis, infectious, cases	Influenza		Measles cases	Meningitis, meningococcus, cases	Pneumonia deaths	Poliomyelitis cases	Scarlet fever cases	Smallpox cases	Typhoid and paratyphoid fever cases	Whooping cough cases
			Cases	Deaths								
NEW ENGLAND												
Maine:												
Portland	0	0	------	0	0	0	1	0	3	0	0	8
New Hampshire:												
Concord	0	0	------	0	0	0	0	0	1	0	0	0
Vermont:												
Barre	0	0	------	0	0	0	0	0	0	0	0	0
Massachusetts:												
Boston	1	0	------	0	10	0	2	16	8	0	0	52
Springfield	0	0	------	0	0	0	0	2	1	0	1	4
Worcester	0	0	------	0	6	0	5	0	0	0	0	3
Rhode Island:												
Providence	0	1	------	0	0	0	0	0	3	0	1	[5
Connecticut:												
Bridgeport	0	0	------	0	0	0	1	1	2	0	0	0
Hartford	0	0	------	0	2	0	0	0	1	0	0	1
New Haven	0	0	------	0	0	0	1	2	0	0	0	4
MIDDLE ATLANTIC												
New York:												
Buffalo	0	0	------	0	0	0	3	8	6	0	0	12
New York	6	3	1	0	17	10	27	78	25	0	10	199
Rochester	0	0	------	0	0	0	3	11	3	0	1	3
Syracuse	0	0	------	0	0	0	1	0	5	0	0	31
New Jersey:												
Camden	0	0	------	0	0	0	1	1	3	0	1	0
Newark	0	0	------	0	2	1	4	3	2	0	0	22
Trenton	0	0	------	0	0	0	1	15	0	0	1	11
Pennsylvania:												
Philadelphia	1	0	------	0	12	2	16	25	7	0	2	72
Pittsburgh	0	0	1	1	1	1	3	6	10	0	1	12
Reading	0	0	------	0	0	0	0	0	0	0	0	0
EAST NORTH CENTRAL												
Ohio:												
Cincinnati	0	0	------	1	3	1	7	5	13	0	1	13
Cleveland	2	0	------	0	0	3	5	7	1	0	0	51
Columbus	1	0	------	0	1	0	3	0	4	0	0	4
Indiana:												
Fort Wayne	0	0	------	0	0	0	2	0	0	0	0	2
Indianapolis	1	0	------	0	1	0	3	3	3	0	0	19
South Bend	0	0	------	0	0	0	0	0	0	0	0	2
Terre Haute	1	0	------	0	0	0	0	0	0	0	0	0
Illinois:												
Chicago	1	0	------	0	40	1	16	33	23	0	2	80
Springfield	0	0	------	0	0	0	0	0	1	0	0	0
Michigan:												
Detroit	4	0	------	0	10	1	6	3	11	0	3	86
Flint	0	0	------	0	0	0	1	0	1	0	0	0
Grand Rapids	0	0	------	0	1	0	0	0	0	0	0	3
Wisconsin:												
Kenosha	0	0	------	0	0	0	0	0	0	0	0	2
Milwaukee	0	0	------	0	4	1	1	2	3	0	0	13
Racine	0	0	------	0	1	0	1	0	0	0	0	7
Superior	0	0	------	0	0	0	0	0	0	0	0	0
WEST NORTH CENTRAL												
Minnesota:												
Duluth	0	0	------	0	1	0	1	0	0	0	0	0
Minneapolis	0	0	------	0	0	0	0	10	3	0	0	2
St. Paul	2	0	------	0	0	1	1	0	1	0	0	25
Missouri:												
Kansas City	0	0	------	0	0	2	5	0	3	0	0	3
St. Joseph	0	0	------	0	0	0	0	0	0	0	0	0
St. Louis	0	1	------	1	1	0	6	4	6	0	2	23

City reports for week ended August 25, 1945—Continued

	Diphtheria cases	Encephalitis, infectious, cases	Influenza		Measles cases	Meningitis, meningococcal, cases	Pneumonia deaths	Poliomyelitis cases	Scarlet fever cases	Smallpox cases	Typhoid and paratyphoid fever cases	Whooping cough cases
			Cases	Deaths								
WEST NORTH CENTRAL—continued												
North Dakota:												
Fargo	0	0	------	0	1	0	1	0	4	0	0	0
Nebraska:												
Omaha	2	0	------	0	0	0	1	2	3	0	0	0
Kansas:												
Topeka	1	0	------	0	0	0	0	0	3	0	0	1
Wichita	0	0	------	0	2	0	1	0	5	0	0	0
SOUTH ATLANTIC												
Delaware:												
Wilmington	0	0	------	0	0	0	2	0	0	0	0	3
Maryland:												
Baltimore	8	0	------	0	1	1	4	3	4	0	0	60
Frederick	0	0	------	0	0	0	0	0	1	0	0	0
District of Columbia:												
Washington	0	0	------	0	0	0	4	17	10	0	1	5
Virginia:												
Richmond	0	0	------	0	0	1	0	24	3	0	3	6
Roanoke	0	0	------	0	0	0	0	0	0	0	0	0
West Virginia:												
Charleston	0	0	------	0	0	0	0	0	1	0	0	0
Wheeling	0	0	------	0	0	0	2	0	1	0	0	0
North Carolina:												
Raleigh	0	0	------	0	0	0	0	0	0	0	0	3
Winston-Salem	0	0	------	0	0	0	0	1	1	0	0	8
South Carolina:												
Charleston	0	0	------	0	0	0	1	0	0	0	0	0
Georgia:												
Atlanta	0	0	------	0	1	0	3	0	1	0	0	0
Brunswick	0	0	------	0	0	0	0	0	0	0	0	0
Savannah	0	0	------	0	0	0	3	0	0	0	0	0
EAST SOUTH CENTRAL												
Tennessee:												
Memphis	0	0	------	0	0	0	10	0	0	0	1	1
Nashville	0	0	------	0	0	0	0	1	0	0	0	0
Alabama:												
Birmingham	0	0	1	0	0	0	2	4	0	0	0	0
Mobile	0	0	------	0	0	0	0	0	0	0	0	0
WEST SOUTH CENTRAL												
Arkansas:												
Little Rock	0	0	------	0	0	0	0	0	0	0	0	1
Louisiana:												
New Orleans	4	0	4	0	4	0	9	2	0	0	2	4
Shreveport	0	0	------	0	0	0	3	2	4	0	0	0
Texas:												
Dallas	4	0	------	0	4	0	3	5	4	0	0	4
Galveston	4	0	------	0	0	0	0	0	0	0	0	0
Houston	1	0	------	0	0	0	3	6	1	0	0	0
San Antonio	0	1	------	0	0	0	6	2	0	0	0	5
MOUNTAIN												
Montana:												
Billings	0	0	------	0	0	0	0	0	0	0	1	0
Great Falls	0	0	------	0	0	0	0	0	0	0	0	0
Helena	0	0	------	0	0	0	0	0	0	0	0	0
Missoula	0	0	------	0	0	0	0	1	0	0	0	0
Idaho:												
Boise	0	0	------	0	0	0	2	0	0	0	0	0
Colorado:												
Denver	1	0	1	0	1	0	6	9	1	0	0	25
Pueblo	0	0	------	0	0	0	1	0	0	0	0	2
Utah:												
Salt Lake City	0	0	------	0	4	0	1	5	3	0	0	6

City reports for week ended August 25, 1945—Continued

	Diphtheria cases	Encephalitis, infectious, cases	Influenza		Measles cases	Meningitis, meningococcus, cases	Pneumonia deaths	Poliomyelitis cases	Scarlet fever cases	Smallpox cases	Typhoid and paratyphoid fever cases	Whooping cough cases
			Cases	Deaths								
PACIFIC												
Washington:												
Seattle	0	0	------	0	5	1	6	1	0	0	0	4
Spokane	2	0	------	0	0	0	0	0	0	0	0	0
Tacoma	0	0	------	0	12	0	0	0	0	0	0	1
California:												
Sacramento	0	0	------	0	7	0	1	1	2	0	0	0
San Francisco	4	0	------	0	20	1	8	1	7	0	0	4
Total	51	6	8	3	175	28	210	322	217	0	34	917
Corresponding week, 1944	34	------	8	6	102	------	208	------	162	0	35	516
Average, 1940–44	36	------	22	[1] 7	[2] 206	------	[1] 216	------	177	0	37	929

[1] 3-year average, 1940–42. [2] 5-year median, 1940–44.

Dysentery, amebic.—Cases: Philadelphia, 1: Chicago, 1: Detroit, 1; St. Louis, 1.
Dysentery, bacillary.—Cases: New Haven, 1; New York, 2; Charleston, S. C., 4; Atlanta, 1: Great Falls, 3.
Dysentery, unspecified.—Cases: Richmond, 1; San Antonio, 8.
Rocky Mountain spotted fever.—Cases: Richmond, 2.
Typhus fever, endemic.—Cases: New York, 2; Winston-Salem, 1: Charleston, S. C., 5: Atlanta, 4: Savannah, 3; Nashville, 1: Birmingham 2; New Orleans, 5; Shreveport, 1; Houston, 8; San Antonio, 5.

Rates (annual basis) per 100,000 population, by geographic groups, for the 84 cities in the preceding table (estimated population, 1943, 32,339,600)

	Diphtheria case rates	Encephalitis, infectious, case rates	Influenza		Measles case rates	Meningitis, meningococcus, case rates	Pneumonia death rates	Poliomyelitis case rates	Scarlet fever case rates	Smallpox case rates	Typhoid and paratyphoid fever case rates	Whooping cough case rates
			Case rates	Death rates								
New England	2.8	2.8	0.0	0.0	50	0.0	27.6	58.0	53	0.0	5.5	213
Middle Atlantic	3.2	1.4	0.9	0.5	15	6.5	27.3	68.0	28	0.0	7.4	168
East North Central	6.1	0.0	0.0	0.6	37	4.3	27.4	32.2	36	0.0	3.6	171
West North Central	9.9	2.0	0.0	2.0	10	6.0	31.8	31.8	66	0.0	4.0	107
South Atlantic	14.1	0.0	0.0	0.0	4	3.5	33.6	79.6	39	0.0	7.1	150
East South Central	0.0	0.0	5.9	0.0	0	0.0	70.8	29.5	0	0.0	5.9	6
West South Central	37.3	2.9	11.5	0.0	23	0.0	68.9	48.8	26	0.0	5.7	40
Mountain	7.9	0.0	7.9	0.0	40	0.0	79.4	119.1	32	0.0	7.9	262
Pacific	19.6	0.0	0.0	0.0	144	6.5	49.0	10.0	29	0.0	0.0	29
Total	8.2	1.0	1.3	0.5	28	4.5	34.0	52.1	35	0.0	5.5	148

PLAGUE INFECTION IN ALPINE AND KERN COUNTIES, CALIF.

Under date of August 23, 1945, plague infection was reported proved in specimens as follows: In tissue from 1 ground squirrel, *C. beldingi*, shot at Hope Valley, Alpine County, Calif., 6 miles west of Woodfords on Carson Pass Highway No. 88, proved positive on August 16; in tissue from 2 ground squirrels, same species, shot at same location, proved positive on August 21; and in a pool of 200 fleas from 34 ground squirrels, *C. beecheyi*, shot on the east side of Castair Lake, Kern County, Calif., proved positive on August 21.

FOREIGN REPORTS

CANADA

Provinces—Communicable diseases—Week ended August 11, 1945.—During the week ended August 11, 1945, cases of certain communicable diseases were reported by the Dominion Bureau of Statistics of Canada as follows:

Disease	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia	Total
Chickenpox		1		24	48	3	14	50	28	168
Diphtheria		3	5	19	4	6		4		41
Dysentery, bacillary				2		1			1	4
German measles					9			12	4	25
Influenza		4			9	1			5	19
Measles		1	1	15	79	4	5	16	28	149
Mumps				15	30	18	3	13	7	86
Poliomyelitis		1			[1] 16				2	[1] 19
Scarlet fever		2	7	23	29	5	2	6	4	78
Tuberculosis (all forms)		6	16	48	51	19	13	71		224
Typhoid and paratyphoid fever			1	4				1	3	9
Undulant fever				3		1		1	2	7
Venereal diseases:										
Gonorrhea		12	38	145	142	58	31	44	122	592
Syphilis		9	5	118	62	10	6	8	39	257
Whooping cough		7		77	32		1	14		131

[1] Includes 2 cases, delayed reports.

REPORTS OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER RECEIVED DURING THE CURRENT WEEK

NOTE.—Except in cases of unusual incidence, only those places are included which had not previously reported any of the above-named diseases, except yellow fever, during the current year. All reports of yellow fever are published currently.

A table showing the accumulated figures for these diseases for the year to date is published in the PUBLIC HEALTH REPORTS for the last Friday of each month.

Plague

Great Britain—Malta.—For the week ended August 18, 1945, 3 cases of plague were reported in Malta, Great Britain.

Morocco (French).—For the period August 11–20, 1945, 50 cases of plague were reported in French Morocco.

Peru.—For the month of July 1945, plague was reported in Peru by Departments as follows: Ica, 1 case; Libertad, 1 case; Lima, 2 cases. Plague infection in rodents was also reported in Huacho and Chuquizongo, Peru.

Smallpox

British East Africa—Tanganyika.—For the week ended July 28, 1945, 181 cases of smallpox with 9 deaths were reported in Tanganyika, British East Africa.

Ceylon.—For the period July 28 to August 12, 1945, 95 cases of smallpox with 15 deaths were reported in Ceylon.

Rhodesia, Northern.—For the week ended July 28, 1945, 482 cases of smallpox were reported in Northern Rhodesia.

Uruguay.—For the month of July 1945, 86 cases of smallpox, including 19 cases previously reported, were reported in Uruguay.

Typhus Fever

Egypt.—For the week ended August 4, 1945, 116 cases of typhus fever with 32 deaths were reported in all of Egypt.

Morocco (French).—For the period August 11–20, 1945, 106 cases of typhus fever were reported in French Morocco, including 1 case reported in Casablanca.

Turkey.—For the week ended August 25, 1945, 27 cases of typhus fever were reported in Turkey, including 2 cases reported in Ankara and 2 cases in Istanbul.

Yellow Fever

Gold Coast—Winneba.—Yellow fever was reported in Winneba, Gold Coast, as follows: August 8, 1945, 1 suspected case; August 22, 1945, 1 new case.

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