iliac apophyses have not appeared will increase with growth. Correction and spine fusion will arrest growth and the curve will not increase.

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RÉSUMÉ

La majorité des scolioses sont d'origine idiopathique ou paralytique. La scoliose congénitale de type classique est causée par une hémivertèbre. On peut aussi observer une fusion des pédicules et des lames d'un côté produisant une courbure. Dans certains cas cette courbure est contrebalancée du côté opposé par une autre malformation, de sorte que la colonne est dite "compensée". La scoliose du nourrisson n'est mentionnée qu'en passant puisqu'elle est rare et que dans plusieurs cas elle semble se corriger spontanément. La forme infantile ou juvénile se découvre chez l'enfant entre trois et six ans et progresse rapidement dans la région dorsale. Elle mène à des difformités sérieuses et répond mal au traitement. La séquelle scoliotique de la poliomyélite peut survenir à tout âge et suivre l'atteinte paralytique de quelques années. Elle présente de graves dangers chez les jeunes malades. Parmi les autres causes citons la neurofibromatose, les affections vertébrales et l'empyème. La forme essentielle de l'adolescence se voit habituellement chez une fillette de 10 à 12 ans, par ailleurs bien portante, et dont les parents consultent après avoir découvert chez elle l'inégalité des épaules et la saillie d'une hanche. Au cours de l'examen clinique la gibbosité thoracique est mise en évidence par la flexion du dos en avant comme pour toucher le sol du bout des doigts. La radiographie confirme et précise aussi quelquefois cet examen; elle doit être prise dans la position debout et toute inégalité dans la longueur des jambes doit être corrigée afin d'obtenir un bassin bien horizontal. Une fois le diagnostic posé il convient d'intervenir puisque la difformité a tendance à s'accentuer au cours de la croissance. Le choix de la vertèbre terminale dans la détermination de la courbure présente souvent quelques difficultés. L'auteur fournit des précisions thérapeutiques tirées de son expérience de 160 arthrodèses vertébrales.

CHRONIC ATROPINIZATION AND FIBROCYSTIC DISEASE OF THE PANCREAS*

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THE PROJECT to be described in this paper was undertaken to determine whether chronic inhibition of glandular secretions by atropine could produce in young puppies a condition similar to fibrocystic disease of the pancreas in children. The syndrome produced by atropine had certain features in common with that of fibrocystic disease. Under the conditions of the experiment, however, chronic atropinization did not produce fibrosis or cyst formation in the pancreas.

The fundamental cause of fibrocystic disease of the pancreas is unknown. It is associated with abnormal function of various exocrine glands, including the acinar glands of the pancreas, bronchial glands, glands of the bile ducts, the sweat glands, and the salivary glands.[1, 2] It has been suggested that dysfunction of the autonomic nervous system may be responsible for these glandular disturbances and, in turn, for the production of fibrocystic disease of the pancreas.[2-4] The initial exploration of this etiological concept, described below, yielded promising but as yet equivocal data in support of the theory.

METHOD

The work was performed upon mongrel puppies. The animals were taken at one to three months after weaning. Their initial mean (± standard deviation) weight was 2.84 ± 0.85 kg. They were of both sexes, and were fed Purina fox chow checkers, bread, milk, meat, and water *ad libitum* with supplements of decavitamin capsules (U.S.P. XV). The required dose of atropine (B.P. 1958) was calculated as mg. per kg. body weight, dissolved in olive oil (B.P. 1958) and injected subcutaneously.

The dose of this preparation which would inhibit the parasympathetic receptors for 24 hours was determined upon 16 puppies. The animals were given a range of doses, from 2 to 50 mg. per kg., and the action of the drug upon heart rate, pupil diameter, pupillary light reflex, nasal moisture (diameter of area absorbed on filter paper) and general clinical activity was recorded. Mydriasis and inhibition of pupillary contraction to light were achieved with a dose of 2 mg. per kg. Complete inhibition of secretion of nasal moisture, i.e. a dry nose, for 24 hours was obtained with a dose of 16 mg. per kg. but not with a dose of 12 mg. per kg.

The dose selected for chronic daily administration was 16 mg. per kg. This dose is larger than the "smallest effective dose" reported originally by Henderson,[5] because complete inhibition lasting 24 hours was desired. From evidence reviewed by Ambache,[6] all cholinergic transmission was not necessarily inhibited even by the dose of 16 mg. per kg.

The relation of this dose to the median lethal dose was determined by measurement of the LD_{50} ± SE in puppies and kittens, after the technique of Boyd.[7] For comparative purposes, the LD_{50} ± SE of atropine sulphate (B.P. 1958) dissolved in distilled water and given subcutaneously was determined in puppies.

Atropine was then given daily, in a dose of 16 mg. per kg. subcutaneously, for seven to 21 days

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TABLE I.—MEASUREMENTS AT THE TIME OF AUTOPSY

Measurement	Units	Control dogs (mean ± st. dev.)	Atropinized dogs: Mean per cent change	Atropinized dogs: P
Body weight	kg.	3.82 ± 1.24	− 32.5	<0.001
Food intake	g./kg./24 hours	58.1 ± 16.0	− 58.6	<0.001
Water intake	ml./kg./24 hours	273.0 ± 148.0	− 57.1	0.005
Pupil diameter	mm.	6.2 ± 0.3	+ 66.7	<0.001
Light contraction of pupil	% contraction of diam.	50.4 ± 1.7	−100.0	<0.001
Nasal moisture	diam. in cm.	1.5 ± 0.5	− 81.1	<0.001
Volume of respiratory tract fluid	ml./kg./24 hours	0.22 ± 0.21	+514.0	0.001
Gastric acidity	pH	4.61 ± 1.49	+ 42.3	0.005
Duodenal reaction	pH	6.83 ± 0.32	+ 0.9	0.7
Bile volume	ml./kg. body weight	1.23 ± 0.77	+295.0	<0.001
Plasma chloride	mEq./litre	105.8 ± 3.2	− 4.6	0.005
Hæmatocrit	ml. cells/100 ml. blood	45.7 ± 8.8	− 12.6	0.05
Plasma neutral fat	mg./100 ml. plasma	56.0 ± 51.0	+ 68.2	0.05
Plasma total cholesterol	mg./100 ml. plasma	80.0 ± 28.0	+ 50.3	0.01
Plasma cholesterol ester	mg./100 ml. plasma	53.0 ± 22.0	− 11.0	0.8
Plasma free cholesterol	mg./100 ml. plasma	27.0 ± 11.0	+170.6	0.001
Plasma phospholipid	mg./100 ml. plasma	202.0 ± 118.0	+ 30.4	0.2
Plasma amylase	units/ml.	496.0 ± 214.0	− 19.4	0.3
Zinc turbidity test	arbitrary units	0.2 ± 0.4	+400.0	<0.001
Urine sugar	arbitrary units	1.3 ± 1.0	+ 7.7	0.8
Urine blood	arbitrary units	0.0 ± 0.0	0.0	1.0
Urine acetone	arbitrary units	0.0 ± 0.0	+ 30.0	0.02
Urine bilirubin	arbitrary units	0.0 ± 0.0	0.0	1.0
Urine albumin	arbitrary units	0.6 ± 0.9	+ 83.3	0.3
Pancreatic trypsin	units/g. of pancreas	174.0 ± 86.0	− 42.0	0.05
Pancreatic acini	diameter in microns	32.1 ± 3.8	− 5.0	0.3
Pancreatic phospholipid	g./100 g. dry weight	10.53 ± 1.03	+ 13.8	0.05
Lung phospholipid	g./100 g. dry weight	7.57 ± 3.55	− 28.0	0.005
Liver free cholesterol	g./100 g. dry weight	0.62 ± 0.11	+ 50.0	0.01

to 17 puppies with 17 littermate controls given an equivalent volume of olive oil. Daily (seven days a week) measurements included those of body weight, food intake (limited to chow), water intake, diameter of the pupil, per cent reduction of pupillary diameter on exposure to a standard light exposure, nasal moisture, and clinical observations as indicated.

At intervals of one to three weeks, pairs (atropinized and control) of animals were anæsthetized with urethane and arranged for collection of respiratory tract fluid[8] over a period of four hours. A sample of heparinized blood plasma was then obtained for the measurement of plasma lipids,[9] chloride,[10] amylase,[11] and the zinc turbidity hepatic function test.[12]

Post-mortem examination was then carried out. The pH of gastric juice and duodenal contents was measured by Fisher alkacid papers. The volume of bile in the gall bladder was determined. The sediment and relative viscosity of bile were measured in one puppy and found to be elevated; specific gravity and pH were about the same as in the control puppy. Urine in the urinary bladder was tested as noted in Table I, using the Ames Diagnostic Kit. Measurements were made of the tryptic activity[13] of the pancreas, and the lipid composition[9] of pancreas, lung, and liver. Wet weight and water levels were determined for the organs and tissues noted in Tables II and III. Histopathological examinations were made upon sections of these tissues stained with hæmatoxylin-phloxine-saffron. The diameter of the pancreatic acini was measured with a stage micrometer.

RESULTS

The median lethal dose of atropine was found to be 125 ± 5 mg. per kg. in puppies and 108 ± 10 in kittens. The corresponding value for atropine sulphate was 181 ± 12 mg. per kg. in puppies. The "lethal dose" of atropine sulphate subcutaneously has been previously reported at 200 to 250 mg. per kg. in dogs.[14] Free atropine base killed the puppies in 38 ± 12 hours; atropine sulphate, in 11 ± 9 hours.

The clinical signs of intoxication in puppies at the range of the median lethal dose were as follows: exophthalmos, mydriasis, asialia, dysphagia, anorexia, adipsia, occasional vomiting, constipation, oliguria, rapid and shallow respiration, tachycardia, occasional hyperthermia, tonic-clonic convulsions, and death due to respiratory failure. At autopsy the lungs were congested, the pH of gastric juice was elevated almost to neutrality, and occasionally bilirubin was found in urine.

Observations on the puppies which were given repeated injections of atropine in a dose of 16 mg. per kg. per day are summarized in Tables I to IV. Vomiting occurred within one hour after the first injection but not after subsequent doses of atropine. The animals appeared withdrawn and dysphonic for two days. The third to seventh injections produced increasing excitement. During the second week diarrhœa, scleritis, blepharitis, purulent rhinitis and nasal dermatitis developed, dysphonia continued, and weakness and prostration became increasingly apparent. There were seven puppies left at 14 days; of these one died on each of the

TABLE II.—THE WEIGHT OF ORGANS AND TISSUES AT AUTOPSY

Organs	Control dogs (mean ± st. dev.) wet weight (grams)	Atropinized dogs: Mean per cent change	P
Thymus gland	8.10 ± 4.78	−82.6	<0.001
Testicles	1.50 ± 1.08	−64.1	0.3
Spleen	10.2 ± 4.58	−52.1	0.005
Pancreas	16.5 ± 5.6	−41.8	<0.001
Heart	29.8 ± 10.1	−41.3	<0.001
Thyroid gland	0.551 ± 0.208	−38.9	0.01
Jejunum	121.8 ± 25.2	−38.7	<0.001
Ovaries	0.545 ± 0.197	−37.4	0.02
Liver	187.3 ± 43.9	−36.6	<0.001
Kidneys	38.2 ± 11.4	−34.6	0.01
Total body weight	3820.0 ± 1240.0	−32.5	<0.001
Lungs	64.1 ± 28.0	−27.0	0.1
Duodenum	3.08 ± 0.89	−26.3	0.02
Right bronchus	0.43 ± 0.19	−26.0	0.05
Œsophagus	10.2 ± 4.2	−17.9	0.2
Adrenal glands	0.822 ± 0.246	−17.1	0.1
Submaxillary salivary glands	2.86 ± 0.378	−10.8	0.1
Gall bladder	0.778 ± 0.266	− 7.4	0.6

15th, 19th, and 20th days and the remainder were killed during the third week.

As noted in Table I, loss of weight and a decrease in food and water intake occurred. The pupil was maximally dilated and failed to react to light throughout; the nose remained dry; the volume output of respiratory-tract fluid was increased. The pH of the stomach was almost neutral, and the volume of bile in the gall bladder at autopsy was increased. Tryptic activity of the pancreas was below normal, as were the hæmatocrit and plasma chloride levels. There was a moderate lipæmia with a decrease in the ratio of cholesterol ester to total cholesterol—cholesterol "Estersturz" which may characterize impaired hepatic function.[15] Impaired hepatic function was suggested further by the finding of increased zinc turbidity. The urinalysis was negative apart from some acetonuria.

TABLE III.—THE WATER LEVEL OF BODY ORGANS AT AUTOPSY

Organ	Control dogs (mean ± st. dev.) g./100 g. dry weight	Atropinized dogs: Mean per cent change	P
Adrenal glands	224 ± 50	+32.9	0.001
Testicles	557 ± 75	+27.9	0.2
Thyroid gland	285 ± 36	+20.5	0.02
Pancreas	296 ± 40	+16.6	0.005
Skin	195 ± 46	+15.3	0.1
Jejunum	375 ± 31	+11.0	0.01
Duodenum	339 ± 35	+ 9.1	0.02
Ovaries	415 ± 56	+ 7.3	0.2
Right bronchus	364 ± 50	+ 7.1	0.001
Liver	288 ± 20	+ 3.7	0.4
Cerebrum	439 ± 24	+ 3.4	0.2
Kidneys	367 ± 41	+ 3.1	0.1
Œsophagus	420 ± 37	+ 1.6	0.8
Rectus abdominis muscle	336 ± 25	− 0.8	0.8
Spleen	376 ± 19	− 1.5	0.5
Cerebellum	422 ± 28	− 1.9	0.7
Lungs	432 ± 31	− 2.9	0.2
Heart	399 ± 18	− 3.1	0.1
Gall bladder	435 ± 97	−10.4	0.1
Submaxillary salivary glands	375 ± 30	−10.7	0.01
Thymus gland	436 ± 90	−11.5	0.3

Lipid levels in the pancreas, lung, and liver were within normal limits, except as indicated in Table I.

At autopsy, all organs were found to have lost weight. As noted in Table II, some organs, such as thymus gland, spleen, pancreas, and heart, lost more weight than others, such as gall bladder and salivary glands.

Changes in water levels of the organs at autopsy are recorded in Table III. The adrenal glands, thyroid gland, pancreas, jejunum, duodenum, and the bronchi were œdematous. The salivary glands were dehydrated.

TABLE IV.—HISTOPATHOLOGIC OBSERVATIONS AT AUTOPSY

Organ	In atropinized dogs	Reported in fibrocystic disease of the pancreas (reference)
Pancreas	Decreased or absent zymogenic granules	22
	Degeneration of acinar cells	22, 24
	Islets of Langerhans normal	1, 16, 19
	Debris in lumen of ducts	2, 16, 22, 24
Lungs	Leukocytic infiltration	2
	Areas of consolidation	1, 19
	Debris in lumen of bronchioles	16, 19, 23
Liver	Fat vacuolation of hepatic cells	1, 19, 24
Gall bladder	Mucosa thin	23
Thymus gland	Loss of thymocytes and reticular atrophy	17
Adrenal glands	Normal	17
Œsophagus	Normal	
Duodenum	Normal	24
Jejunum	Normal	24
Ileum	Intussusception in 18% of animals	25
Spleen	Normal	
Kidneys	Normal	17
Heart	Normal	
Salivary glands	Normal	23
Thyroid gland	Normal	17
Skeletal muscle	Normal	
Cerebrum	Normal	17
Cerebellum	Normal	17
Skin	Normal	

The histopathological findings are summarized in Table IV. Outstanding were early degeneration of the acinar cells of the pancreas, pneumonic-like consolidation of the lungs, early fatty degeneration of the liver, early atrophy of the thymus gland, and the occasional appearance of intussusception.

The chronic administration of atropine, therefore, produced in puppies a syndrome characterized by protracted cholinergic inhibition, stimulation followed by depression of the central nervous system, loss of weight, and increasing cachexia. There was impairment of several organs, such as the gastrointestinal tract, pancreatic acinar glands, liver, and thymus gland. The lungs showed pneumonic-like congestion, and the output of respiratory tract fluid was increased. There was a disturbance of salt and water metabolism characterized by a hypochlorædmia and œdema of several organs.

DISCUSSION

The syndrome of chronic atropinization in puppies was compared with the corresponding syn-

drome in published reports upon fibrocystic disease of the pancreas. Clinical signs in atropinized puppies that have been reported also in fibrocystic disease include reduction of weight gain,[1] diarrhœa,[16] vomiting,[16] and blepharitis.[17] Serum chloride level has been reported normal to low,[18] duodenal pH unchanged,[1] duodenal tryptic activity reduced,[19] serum amylase activity normal,[20] serum free cholesterol high,[21] serum cholesterol ester low,[21] serum zinc turbidity increased,[21] and urinalysis essentially negative[1] in fibrocystic disease of the pancreas. In these respects, the two syndromes are alike. The dry skin, dilated pupil, and loss of gastric acidity of atropinization do not occur in fibrocystic disease.

Many histopathological features found at autopsy in puppies given daily doses of atropine have also been reported to occur in fibrocystic disease of the pancreas. A sample of references to such reports has been included in Table IV.

The following pathological changes occur in fibrocystic disease but were not encountered in the atropinized puppies: pancreatic cysts,[1] fibrous and fatty tissue replacement of pancreatic acini,[1] metaplasia of bronchial epithelium,[16] fibrocystic bile ducts,[23] mucosal cysts in the gall bladder,[22] cysts in the intestinal mucosa,[23] and focal necrosis of skeletal muscle.[26]

The following were found in atropinized puppies at autopsy and have not been reported to date in fibrocystic disease of the pancreas: an increased volume of bile in the gall bladder, decreased tryptic activity of pancreatic tissue, decreased hæmatocrit, increased plasma neutral fat, no change in the diameter of pancreatic acini, increased pancreatic phospholipid, decreased lung phospholipid, increased liver free cholesterol, and relative changes in weight and water levels of the organs of the body.

It is evident, therefore, that the two syndromes have much in common. The outstanding difference was the absence of fully developed acinar cysts and replacement of acini by fibrous tissue in the pancreas. There was evidence of degeneration of the pancreatic acini in the atropinized puppies. It is possible that administration of atropine in smaller daily doses for a longer period of time might produce a typical fibrocystic change in the pancreas.

SUMMARY

Atropine was given subcutaneously in a dose of 16 mg. per kg. daily for one to three weeks to young puppies and the syndrome produced was compared with that of fibrocystic disease of the pancreas in children. The atropinized puppies developed a cachexia clinically similar to that seen in advanced fibrocystic disease. Significant decreases were found in body weight gain, food and water intake, nasal moisture, pancreatic tryptic activity, plasma chloride, hæmatocrit, lung phospholipid, weight of most organs, and water level of salivary glands. There were significant increases in pupil diameter, output of respiratory tract fluid, gastric pH, bile volume, plasma neutral fat, plasma total cholesterol, plasma free cholesterol, plasma (hepatic) zinc turbidity reaction, urinary acetone, pancreatic phospholipid, liver free cholesterol, and the water level of many organs. No significant changes were noted in duodenal pH, plasma ester cholesterol, plasma phospholipid, plasma amylase, urinary sugar, urinary blood, urinary bilirubin, urinary albumin, and the diameter of the pancreatic acini. At autopsy there was degeneration of the pancreatic acini but no cysts or replacement of acini by fibrous tissue. Areas of consolidation in the lungs, degenerative changes in the liver, gall bladder, and thymus gland and a high incidence of intussusception were present. Atropinization, therefore, produced a syndrome in puppies similar in many, but not all, respects to that of fibrocystic disease of the pancreas in children.

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RÉSUMÉ

Une dose quotidienne de 16 mg./kg. d'atropine en injection sous-cutanée administrée à des jeunes chiens pendant une à trois semaines a produit chez ces animaux un syndrome qui ressemble à la maladie fibro-kystique des enfants. La cachexie chez ces chiots évoquait le tableau clinique que l'on voit à un stage avancé de la fibrose kystique du pancréas. On observa un retardement de la croissance, une perte d'appétit, une sécheresse de la muqueuse nasale, un abaissement de l'activité tryptique dans le pancréas, du taux des chlorures plasmatiques, de l'hématocrite, des phospholipides pulmonaires, du poids de la plupart des organes et de la concentration d'eau dans les glandes salivaires. Par contre on vit aussi une dilatation pupillaire, une augmentation des secrétions bronchiques, une élévation du pH gastrique, du volume de secrétion biliaire, du taux des graisses neutres du plasma, du cholésterol plasmatique total et aussi libre, de l'acétone urinaire, des phospholipides pancréatiques, du cholésterol libre dans le foie, de la teneur d'eau de plusieurs organes et enfin une réaction plus accusée dans l'épreuve de la turbidité du zinc plasmatique. Les données suivantes demeurèrent inchangées: le pH du duodénum, le cholestérol estérifié, les phospholipides et l'amylase du plasma; le sucre, le sang, la bilirubine et l'albumine dans l'urine et enfin, le diamètre des acini. La confrontation anatomique montra une dégénérescence des acini, mais sans formations kystiques ou remplacement par du tissu fibreux. Il y avait des zones de consolidation dans les poumons, de dégénérescence dans le foie, la vésicule biliaire et le thymus, ainsi que de fréquentes invaginations intestinales.