cases was worry and anxiety, often arising from circumstances—domestic, financial, etc.—already present in civil life and carried with the man into the Army. In other cases the source of worry was associated with the war, although not with Army routine. It is not always realized that the soldier in this war has the same sources of worry as are so universal among the civilian population; thus very many men are anxious about their wives and parents in bombed areas, or about their families evacuated to unfamiliar surroundings. Then there are men who have left good civilian positions for much less remunerative Army service, not all having their pay made up; others have had their training for a skilled but non-essential occupation interrupted and are apprehensive of the future. Army life itself gives few causes of worry, as the soldier is well looked after; but undoubtedly some men worry about the uncertainty of when their next move will be made and where it may take them. It seems reasonable to suggest that anxiety may play a part in the production of dyspepsia in men whose autonomic nervous system is constitutionally somewhat precariously balanced, especially as it is agreed that worry has an adverse influence on the symptoms of established peptic ulcer. In pointing out the factor of anxiety it is not suggested that those men suffered from anxiety neurosis: quite the contrary, as with them, unlike cases of anxiety neurosis, there was adequate cause for worry. Nor was the anxiety of pathological intensity or such as to interfere with their general efficiency: such men were never medically "boarded," and simple measures were sufficient to fit them for duty. They were firmly assured that they did not suffer from any organic disease and that their health was good and would improve under Army conditions. In only a few cases were medicines—e.g., acid, hydrochlor. dil. or magn. trisilicat.—necessary. Details of the findings were always sent to the unit M.O.

The incidence of actual neurosis was very low; 9 of the 11 cases arose in civil life and were unchanged by Army service, save possibly for the better. The incidence of chronic cholecystitis and gastric carcinoma is much lower than in a civil hospital, probably owing to the lower average age of our patients.

Conclusion

This analysis shows that the problem of dyspepsia in the Army is more or less the same as that of peacetime civil life, any differences being determined by such factors as age groups, sex, general anxiety about the war, etc. Army conditions have not produced any new syndrome, and it is very probable that they have not increased the incidence of gastric or duodenal ulcer. The increased incidence of dyspepsia in the Army of this war finds its parallel in a comparable increase in the civil population since the last war, and is directly related thereto.

Summary

257 cases presenting symptoms of dyspepsia were seen at a military hospital during a period of four months. Of these, 212 are considered in detail.

The incidence of peptic ulcer was similar to that found in civil hospitals.

There is an increased incidence of functional dyspepsia, the aetiology of which is discussed.

The analysis does not reveal that Army conditions have any marked effect on the production of dyspepsia.

Thanks are due to Colonel R. G. Gordon, A.M.S., officer commanding, for permission to publish this paper, and for his encouragement during its preparation.

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GASTRO-PAPILLOMATOSIS DUE TO VITAMIN A DEFICIENCY INDUCED BY HEATED FATS*

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Since Fibiger (1913) first described experimentally induced tumours of the fore-stomach of the rat many other workers have investigated this problem without, however, reaching a satisfactory explanation of his original results. Fibiger described three types of lesions: (a) multiple papillomata of the fore-stomach; (b) squamous carcinoma of the fore-stomach; and (c) carcinoma of the tongue. He also obtained a carcinoma in a mouse that was transplantable. These lesions he attributed to the presence of a nematode, *Gongylonema neoplasticum*, derived from cockroaches which were present in the animal-house and which were consumed by the rats in addition to their diet of white bread and water. Passey (1934) drew attention to the fact that such diet must have been deficient in vitamins, and that vitamin A deficiency in the absence of the gongylonema can lead to papillomatosis of the fore-stomach of the rat. Cramer (1937) reviewed experimental work, including his own investigations bearing on Fibiger's results, and concluded that "diet and parasite are in themselves not sufficient to account for the lesions observed by Fibiger, and that there must be yet another factor involved which has not yet been identified." More recently Roffo (1938, 1939) claimed to have obtained a wide range of pathological lesions, including ulcers, papilloma, and carcinoma of the fore-stomach, adenocarcinoma of the glandular stomach, and sarcoma of the stomach and liver, in rats fed with heated or ultra-violet-irradiated cholesterol, and with overheated animal and vegetable fats. It is clear from the copious illustrations to his papers that Roffo has induced marked hyperplasia of the epithelium of both parts of the rat's stomach, amounting in some cases to histological evidence of malignancy, though the carcinomata do not seem to have metastasized to the liver, as might have been expected. The sarcomata, however, metastasized freely. These experiments are therefore of outstanding interest and demand independent investigation. Roffo believes that carcinogenic hydrocarbons are formed from sterols by the action of heat or ultra-violet rays, but, according to Cook and Kennaway (1940), his views on the nature of the chemical changes involved are inadequately supported by his experimental evidence. The presence of carcinogenic hydrocarbons in the food has been shown by Waterman (1939) to be capable of inducing tumours in the fore-stomach of mice.

In this laboratory an examination of a variety of fats has been made, after different conditions of heating, for the possible presence of known carcinogenic hydrocarbons, but nothing having the characteristic fluorescent spectrum of these substances has yet been demonstrated. It seems possible, therefore, that other types of carcinogen may be partly responsible for Roffo's experimental results. The suggestion that ordinary cooking fats may develop carcinogenic properties under the action of heat raises a practical problem which might have a bearing on the incidence of gastric cancer in man. The fats used in Roffo's experiments were apparently heated to 300-400° C., a higher

* Communicated to the Pathological Society of Great Britain and Ireland at Glasgow on July 4, 1941.

† Working under a full-time grant from the British Empire Cancer Campaign.

range of temperature than is ordinarily reached in domestic cooking, but it seemed possible that similar changes might occur progressively in fats repeatedly heated at lower temperatures. Even in times of peace economic conditions habitually forced a large part of the community to use fats repeatedly for cooking, and our experiments were therefore designed to imitate the worst conditions of frying likely to be in daily use, and to test the fats so treated by feeding them to rats and mice.

Experimental

1. A mixed cooking fat (equal parts of cotton-seed oil and whale oil) was heated to 200-220° C. in a closed iron saucepan for twenty to thirty minutes on thirty consecutive weekdays. The total time of heating amounted to about twelve hours. White bread was fried each day in this fat, allowed to cool, and then fed to 50 Norwegian hooded rats, maintained on a basal diet of whole oats, green vegetables, and water, with the addition of about 2 c.cm. of milk per rat three times a week and 2 grammes of carrot once a week after the first two months. When this experiment had been in progress for twelve months 40 rats had died, of which 8 showed multiple papillomata—6 with central ulceration—1 had a single un ulcerated papilloma, and 2 showed irregular hyperplasia of the epithelium, all the lesions occurring in the fore-stomach. One rat developed a carcinoma of the lower lip. As in the foregoing experiment the bread was heated as well as the fat, this variable factor was eliminated in subsequent work by heating the fats alone and, after cooling, spreading them on white bread for feeding to the animals, using unheated fat spread in similar amounts as a control. The survivors of this first group of rats were fed in this manner for a further period of seventeen months, with the addition of about 2 grammes of carrot per rat four times a week, for reasons given below.

2. Twenty-four inbred Wistar albino rats were fed on the basal diet, with the addition of pure lard heated on thirty consecutive weekdays to 200-220° C. for twenty to thirty minutes.

3. Twenty-four Wistar rats were fed on the same basal diet, with the addition of cotton-seed oil, heated in the same way.

4. Twelve Wistar rats were fed on the basal diet, with the addition of unheated lard.

5. Twelve Wistar rats were fed on the basal diet, with the addition of unheated cotton-seed oil. (In Groups 2 to 5, after two months, 2 grammes of carrot once a week, and after a further five months four times a week, was added to the diet.)

6. Fifty stock mice were fed on the basal diet, with the addition of repeatedly heated mixed cooking fat spread on white bread, as described in the second paragraph under Group 1. (After two months 0.5 gramme of carrot once a week, and after a further ten months six times a week, was added to the diet.)

Litters of rats were divided between Groups 2 to 5 so that the groups were genetically comparable. During the first year of these experiments symptoms suggestive of avitaminosis-A were observed in young rats, particularly in Groups 2 and 3. The difference between these groups and the controls became more marked as time passed. The animals were smaller and less robust than the controls, had dry fur and slight xerophthalmia, and avoided exercise except in pursuit of food. As the control animals showed no such symptoms it seemed that the addition of heated fat had in some way neutralized or interfered with the metabolism of the dietary vitamin A. This possibility was tested in the following manner:

7. Twenty-four Norwegian hooded rats were fed on the basal diet, with the addition of about 3 c.cm. of milk and about 2 grammes of carrot once a week. This diet cannot be considered deficient in vitamin A. After four days the following additions to the diet were made: (a) 6 rats received 0.5 gramme of unheated lard six days a week; (b) 6 rats received 0.5 gramme of lard heated at 327° C. for one hour six days a week; (c) 6 rats were similarly fed with lard heated at 220° C. for twelve hours; and (d) 6 rats were similarly fed with lard heated at 220° C. for one hour. After two months 2 rats from each group were killed and their livers rapidly removed, rinsed in physiological saline,

minced, and desiccated. One gramme of desiccated liver was shaken with 5 c.cm. of chloroform for five minutes, the extract was then decanted, and dilutions of 1/1, 1/2, 1/4, up to 1/128, with chloroform, were made in a series of test-tubes. To each tube, containing 0.5 c.cm. of extract, 2 c.cm. of 30% solution of antimony trichloride in chloroform was added, and the highest dilution in which the blue vitamin A colour reaction could be detected was noted. The results of these estimations are shown in Table I.

TABLE I.—Relative Vitamin A Contents of Rat Livers

Rat No.	Lard	Vitamin A Content of Liver (Control = 1)
375B 376B	Unheated (control)	1 1
372B 373B	Heated, 220° C. 1 hr.	1 1
363B 366B	Heated, 220° C. 12 hrs.	1/2 1/2
361B 362B	Heated, 327° C. 1 hr.	1/4 1/8

It will be seen that the vitamin A content of the liver was reduced in proportion to the degree and duration of heating to which the lard was subjected. The remaining rats in this experiment were then fed for one month on a diet rich in vitamin A (basal diet, plus 2 grammes of carrot daily); one from each group was sacrificed, and the liver vitamin A estimated in the above manner. No differences were found between them, showing that the interference with vitamin A metabolism due to the heated lard was not permanent. The remainder of the animals are still under observation.

When animals died their stomachs were washed out and then filled with 10% formol-saline and left to fix for twenty-four hours before being opened. Fixation in this way gave very satisfactory preparations, free from distortion. All the stomachs were subjected to independent histological examination by Dr. L. Woodhouse Price, who reported his findings without knowing the details of the experiment. This is the routine procedure with all histological material in this laboratory. All but three lesions classed as papilloma were histologically confirmed. The results are shown in Tables II to V.

TABLE II.—Lesions in 14 out of 44 Norwegian Hooded Rats, surviving for More than 4 Months, fed on Basal Diet and repeatedly Heated Mixed Cooking Fats (30 Died without Gastric Lesions)

Rat No.	Duration of Experiment at Death	Lesions
108B	139 days	9 papillomata (5 ulcerated) in fore-stomach
138B	182 "	15 " (ulcerated) "
112B	221 "	4 " " "
113B	225 "	4 " " "
122B	226 "	1 papilloma " "
141B	236 "	1 " " "
127B	268 "	21 small papillomata " "
103B	275 "	1 ulcerated papilloma " "
144B	301 "	Marked hyperplasia of fore-stomach "
148B	312 "	Hyperplasia of fore-stomach "
149B	318 "	Haemorrhage in fore-stomach "
150B	343 "	Keratizing carcinoma of lower lip "
128B	354 "	2 haemorrhagic ulcers in glandular stomach "
105B	436* "	Haemorrhage in glandular stomach "

* On vitamin-A-rich diet after first year.

TABLE III.—Gastric Lesions in 6 out of 19 Wistar Rats, surviving for More than 4 Months, fed on Basal Diet plus repeatedly Heated Lard (13 Died without Lesions)

Rat No.	Duration of Experiment at Death	Lesions
741	139 days	2 ulcerated papillomata of fore-stomach
873	192 "	3 " " "
877	209 "	2 papillomata (1 ulcerated) "
694	304 "	4 ulcerated papillomata "
713	304 "	3 " " "
714	315 "	1 papilloma " "

TABLE IV.—*Gastric Lesions in 3 out of 14 Wistar Rats, surviving for More than 4 Months, fed on Basal Diet plus repeatedly Heated Cotton-seed Oil (11 Died without Lesions)*

Rat No.	Duration of Experiment at Death	Lesions
878	117 days	1 ulcerated papilloma of fore-stomach
969	196 "	1 " " "
715	318 "	1 " " "

TABLE V.—*Gastric Lesions in 3 out of 45 Stock Mice surviving for more than 4 Months, fed on Basal Diet plus repeatedly Heated Cooking Fat (41 Died without Lesions; 1 Survives)*

Mouse No.	Duration of Experiment at Death	Lesions
1104	271 days	1 papilloma of fore-stomach
1106	279 "	1 " " "
1134	385 "	Diffuse hyperkeratosis of fore-stomach

In the three groups of rats receiving repeatedly heated fats in addition to the original basal diet 77 survived for more than four months, and 17 of these died within the first year of the experiment and had papillomata in the fore-stomach. Control rats (receiving unheated fats) dying within the same period showed no papillomata, but 2 had minor degrees of hyperplasia. Among 25 old rats (over 2 years) from other experiments 3 showed hyperkeratosis of the fore-stomach, 1 diffuse hyperplasia, and 1 a simple papilloma of the fore-stomach. In our experience similar lesions have not been observed in control rats under 2 years old.

The benzidine test was carried out on stomach contents in cases showing brownish discoloration of the glandular stomach, and was found to be positive, confirming the presence of blood in the stomach cavity, probably derived from small ulcers. Papillomata, ulceration, and consequent haemorrhage appear to be definitely related to the feeding of repeatedly heated fat and associated with symptoms of varying degrees of avitaminosis-A. To test the possible interrelation between these pathological states 10 rats that had been under experiments for a year and 31 for seven months were given a diet rich in vitamin A, consisting of rat-cake nuts (see accompanying formula) daily, carrot 2 grammes four times a week, and about 2 c.cm. of milk once a week, while continuing to receive the differently treated fats as before. Six of these rats died after being on the vitamin-A-rich diet for more than a year, and none of these showed any gross lesion of the stomach. Two survivors are still under observation. The others are accounted for in the tables.

Rat-cake Formula (Supplied by the North-Eastern Agricultural Co-operative Society, Ltd., Bannermill Place, Aberdeen)

Wheat offal (fine middlings No. 2)		19.2%
Ground wheat		19.2%
Sussex ground oats		19.2%
Ground barley		9.5%
Ground maize		9.5%
Meat and bone meal (45% protein)		9.5%
Dried skim-milk		7.0%
White fish meal (60% protein)		4.7%
Dried yeast (40% protein)		1.2%
Sodium chloride		0.5%
Cod-liver oil		0.5%

In more recent experiments 92 rats have been maintained for ten months on the vitamin-A-rich diet throughout, with the addition of heated lard (350° C. for one hour or 220° for about twelve hours). No pathological lesions of the stomach have been observed among 10 that have died. *In vitro* tests for vitamin A in mixtures of cod-liver or halibut-liver oil and heated fats dissolved in chloroform were carried out to see whether any direct neutralization occurred, but the usual antimony trichloride blue reaction could not be observed, as the heated fats alone gave a brilliant red colour reaction with this substance. Attempts to separate the vitamin A from the heated fats after mixture were not successful, and it is not certain at present whether any direct destruction of vitamin A by heated fats occurs or whether the vitamin reaction is merely masked by the intensity of the red colour reaction. Further work is being done to clear up these points and to determine the nature of the substance in the heated fat responsible for the red colour reaction with antimony trichloride.

Discussion

The foregoing evidence suggests that there is present in repeatedly heated fats a factor which interferes in some way with the absorption or metabolism of vitamin A. Our results confirm Roffo's claim that heated fats cause papillomatosis in the fore-stomach of rats, but no evidence of glandular tumours or of sarcoma has been found. One rat developed a carcinoma of the lower lip, but the significance of a single case cannot be assessed.

Although no recognizable carcinogenic hydrocarbons were formed in heated fats under the conditions of our experiments, a factor which may provisionally be termed "anti-vitamin A" was produced, and the subsequent pathological lesions developed by rats and mice receiving this factor with an otherwise adequate diet were apparently due to an artificially induced avitaminosis-A. Thus our results correlate those of Cramer and of Passey with some of the results observed by Fibiger and by Roffo. The malignant tumours originally described by Fibiger and the more extensive series of Roffo may have been due to the action of some hitherto unrecognized factors in the presence of avitaminosis-A. Mice were less susceptible to induced avitaminosis-A and papillomatosis than rats.

So far as any application of these experiments to human pathology is concerned there is no evidence of the development in fats, under ordinary cooking conditions, of any known carcinogen, but the anti-vitamin-A factor may possibly be detrimental to health, particularly when the dietary intake of vitamin A is low. If there is any analogy between rats and humans in this respect the addition of vitamin A to the diet in the form of raw carrot seems to be sufficient to counteract the effects of the anti-vitamin. The habit of eating raw carrot seems to be prevalent at the present time, and it is possible that future statistics will show whether this has any influence on the incidence of human gastric diseases.

Summary

Groups of rats and mice were fed with a variety of repeatedly heated fats in addition to an adequate basal diet. Within a year signs of avitaminosis-A appeared among the rats, and cases of ulceration and papillomatosis of the fore-stomach were observed among those that died. Control animals fed with unheated fats and the same basal diet showed no gross pathological lesions. Extracts of the livers of rats fed with lard heated under various conditions in addition to the basal diet contained reduced amounts of vitamin A as compared with controls.

The heated fats did not contain recognizable amounts of any known carcinogen, but they included some substance which interferes with the antimony trichloride reaction for vitamin A, giving a bright red coloration.

Rats fed with repeatedly heated fats in addition to a diet rich in vitamin A (carrot) showed no gross pathological lesions in fore-stomach or reduction in liver vitamin A.

The mechanism of papillomatosis in these experiments seems to be related to an induced avitaminosis-A, due to the presence in repeatedly heated fats of an "anti-vitamin A" of undetermined nature.

We wish to acknowledge the valued help given by Dr. L. Woodhouse Price in dealing with a large number of histological preparations, and by Mr. J. G. Chalmers in examining fluorescence spectra of extracts of heated fats.

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