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Gastric Pathology Produced by Hypothalamic Lesions in Rats[1]

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LINDHOLM, E., G. SHUMWAY, C. GRIJALVA, T. SCHALLERT AND M. RUPPEL. *Gastric pathology produced by hypothalamic lesions in rats.* PHYSIOL. BEHAV. 14(2) 165–169, 1975. – Rats made aphagic and adipsic by damage to the lateral hypothalamus develop gastric lesions and lose body weight excessively over a four day period. Control observations indicate that these effects cannot be accounted for by food and water deprivation or by operative trauma. The possibility that gastric lesions may contribute to aphagia or anorexia is discussed.

LH Lesion Aphagia Gastric pathology

RATS ulcerate in response to a variety of stress procedures including restraint [1, 2, 3], shock [8, 13, 20], and food deprivation [20]. Brain lesions or electrical stimulation can also affect gastric functioning. In guinea pigs, lesions of the hypothalamus produce gastric pathology within 24 hr [15, 16]. In monkeys stomach pH drops more than four units within 1 hr following brief electrical stimulation of the anterior hypothalamus [22]. In cats, gastric pathology appears within 8 hr following brief electrical stimulation of the anterior hypothalamus or preoptic region [7], and in rats, electrical stimulation of the lateral hypothalamus increases gastric secretion [17].

Data from other sources indicate that profound abnormalities of ingestive behaviors can occur in rats after lesions in a variety of brain loci. Aphagia and adipsia have been reported following lesions of the pallidofugal fibers [18], certain areas of the midbrain [21], and the internal capsule [10]. Cutting fibers just lateral to the lateral hypothalamus (LH) produces similar effects [11], as does neocortical damage [5]. Large lesions of the LH produce such long term aphagia and adipsia that rats will die if not artifically maintained [29], while smaller lesions of the same region produce shorter duration effects [23,29].

It is surprising that no systematic attempt has been made to study gastric pathology following brain lesions which produce feeding abnormalities, particularly since the hypothalamus has been previously implicated in the formation of ulcers [7, 9, 15, 16]. The present experiment demonstrates that large lesions involving the LH produce gastric pathology within 24 hr, and the possible relevance of these data to ingestive behaviors is discussed.

METHOD

Animals

Animals were 84 Holtzman-derived male albino rats weighing 200–350 g which were food but not water deprived for 24 hr. Under barbiturate anesthetic, 32 sustained bilateral lesions involving the LH, 20 sustained control lesions of the thalamus, and the remaining 32 served as unoperated controls. Rats were assigned to groups such that the mean body weight of all groups were approximately equal.

Procedure

Lesions were made with a Stoelting constant current lesion maker. LH stereotaxic coordinates were 2.4 mm posterior to bregma, 1.9 mm lateral to the midline suture, and 8.5 mm below the surface of the horizontal skull. The thalamic control lesion coordinates were the same except the electrode was lowered to 6.5 mm below the skull surface. In all cases, the electrodes were size 00 stainless steel insect pins insulated except for the cut tip, and lesion parameters were 2 mA for 20 sec. Since the uninsulated portion of our electrodes was quite small, these parameters were necessary to produce reasonably complete destruction of the LH.

Following surgery, all rats were returned to individual home cages and a known amount of food (Wayne Lab Bloks) and water was made available to the LH lesioned animals. Of the 20 control lesioned rats, 12 were given food and water ad lib postoperatively while the remaining 8 were

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totally deprived. The unoperated control rats were also totally deprived; these served as deprivation controls for the LH lesioned animals which neither ate nor drank postoperatively.

Subgroups of 8 LH lesioned and 8 unoperated control rats were sacrificed every 24 hr for 4 days using a lethal dose of barbiturate administered intraperitoneally. The unperfused stomachs were quickly removed, opened along the greater curvature, examined for the presence of food, and placed in Formalin solution. The brains of the LH lesioned rats were also removed, preserved, and later sectioned at 38 microns by the cryostatic method and stained with cresyl violet. Of the 12 ad lib control lesioned rats, 4 were sacrificed at 24 hr, 48 hr, and 96 hr postoperatively. Of the 8 control lesioned rats which were deprived, 4 were sacrificed at 24 hr and 4 at 96 hr postoperatively. These stomachs and brains were treated as described above.

Each stomach was pinned flat to a wax slab, photographed, and enlarged 4x actual size. Stomach pathology was scored in the following manner: each discontinuity in the gastric mucosa, whether an ulcer or an erosion, was considered a gastric lesion. Using a millimeter scale overlaying the enlargement, each lesion less than 1 mm in the longest dimension received a score of 1. Similarly, lesions between 1 and 3 mm each received a score of 2, lesions between 3 and 5 mm each received a score of 3, and lesions greater than 5 mm each received a score of 4. This scheme was decided upon after considering the schemes used by others to rate the severity of gastric pathology [1, 2, 3, 8, 19, 20]. Our scheme is conservative in that it ignores hemorrhages and does not proportionally weight lesions larger than 5 mm diameter.

An estimate of errors of measurement was available since three persons independently examined all photographs with all identifying marks obliterated. Reliability of measurement was evaluated by Kendall's Test for Concordance [26] which indicated that the obtained degree of agreement among the three examiners could have occurred by chance less than one time in a thousand. A given rat's gastric lesion score represents the mean of the three scores reported by three independent examiners. Since the mean gastric lesion scores were not normally distributed, the medians of these means are reported and non-parametric statistics were performed. Body weight data were normally distributed and evaluated by *t*-test.

RESULTS

None of the LH lesioned rats ate or drank a measurable quantity during the postoperative observation periods, and their stomachs were empty at autopsy. Figure 1 shows, in agreement with a previous report [20], that deprivation alone produces gastric lesions which increase in severity over days. Of primary interest, however, are the observations of greater gastric pathology in the LH lesioned groups. The LH lesioned rats had higher gastric lesion scores than the comparably deprived unoperated controls ($p = 0.002$ at 24 hr and 48 hr; $p = 0.027$ at 72 hr, by Mann-Whitney U) although the differences were marginal at 96 hr ($p = 0.058$). The thalamic lesioned control groups which were food and water deprived postoperatively attained median gastric lesion scores of 5.2 at 24 hr and 12.8 at 96 hr. These scores are very similar to those of the unoperated groups displayed in Fig. 1 and do not differ significantly from them. By contrast, the LH lesioned group had a higher gastric lesion

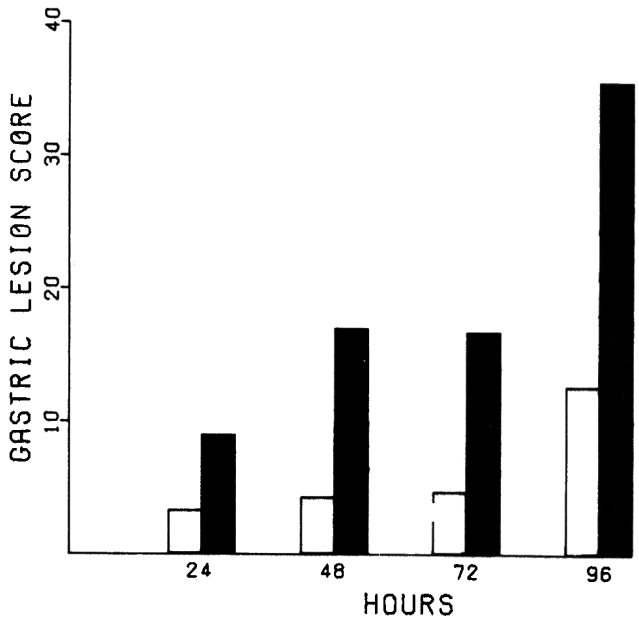

FIG. 1. Median gastric lesion scores as a function of postoperative days. Solid bars, LH lesioned groups. Open bars, unoperated deprived groups.

score than the thalamic lesioned group at 24 hr ($p = 0.024$), but at 96 hr, the differences were not reliable ($p = 0.11$). Finally, the thalamic lesioned control groups which were permitted to eat and drink postoperatively attained median gastric lesion scores of 5.0 at 24 hr, 3.4 at 48 hr, and 3.3 at 96 hr. Again, these scores are reliably lower than those attained by the LH lesioned groups ($p = 0.024$, $p = 0.001$, $p = 0.001$, respectively) but do not differ significantly from the unoperated control groups. The decrease in gastric lesions over days for this group suggests that the presence of food and water in the stomach may have promoted healing and/or prevented the formation of additional ulcers.

In the majority of cases, gastric lesions were observed in both the rumenal and glandular portions of the stomach. Pathology confined exclusively to the rumen was observed in only 5 percent of the rats in the LH lesioned groups and 6 percent of the rats in the deprived, unoperated groups. This is interesting since others [20] have argued that food deprivation produces ulcers confined to the rumen. However, in the present experiment, rats in the deprived, unoperated groups were deprived of water as well as food, and those in the LH lesioned groups neither ate nor drank postoperatively. Additionally, unpublished observations from our laboratory indicate that water deprivation with food available ad lib produces lesions in both the glandular and rumenal protions of the stomach. Thus, in the present experiment, the appearance of lesions in both regions of the stomach must be related to the absence of water intake.

In addition to the greater gastric pathology, LH lesioned groups lost reliably more body weight than either the deprived control lesioned or unoperated groups at each of the 4 postoperative observation periods ($p<0.01$ in all comparisons, *t*-test). Similar observations have been made by others [18,28] and it has been suggested [28] that the greater weight losses may be due to increased metabolism in LH lesioned rats. In the present experiment, the mean

percent body weight losses for the LH lesioned groups were 9.5, 17.1, 23.3, and 28.5 percent for the 24 hr, 48 hr, 72 hr, and 96 hr observation groups, respectively. Comparable figures for the food and water deprived controls were 7.1, 11.5, 18.8, and 23.2 percent. Similarly, the deprived control lesioned groups sustained losses of 7.6 percent at 24 hr and 21 percent at 96 hr.

Photographs of stomachs are presented in Figs. 2 and 3. In Fig. 2 is shown a stomach taken from an LH lesioned rat 48 hr postoperatively. This specimen was selected since its gastric lesion score, which was 20, represents the midpoint of the ordinate of Fig. 1. One rumenal lesion is obvious, but numerous small lesions of the glandular portion of the stomach, which were apparent under 4× magnification, are not readily apparent in this reduced photograph. In Fig. 3 is shown an extreme case taken from the 96 hr LH lesioned group. In this specimen, lesions are apparent throughout the body and rumen of the stomach.

The brain lesions which produced the abnormal stomachs shown in Figs. 2 and 3 are shown in Figs. 4 and 5, respectively. With reference to the König and Klippel atlas [14], the mean (and median) LH lesion extended from Plates 32 to 40 and extremes reached anteriorally to Plate 16 and posteriorally to Plate 47. The mean (and median) lesion was approximately 1.5 mm long and 1 mm in the medial–lateral and dorsal–ventral planes estimated from the section of maximum damage. In addition to the LH, lesions frequently involved the ventro-medial portion of the internal capsule, Fields of Forel, fornix, and occasionally the optic tract. Control lesions extended from Plates 26 to 42 and involved the ventral, lateral, and medial thalamic nuclei as well as the internal capsule.

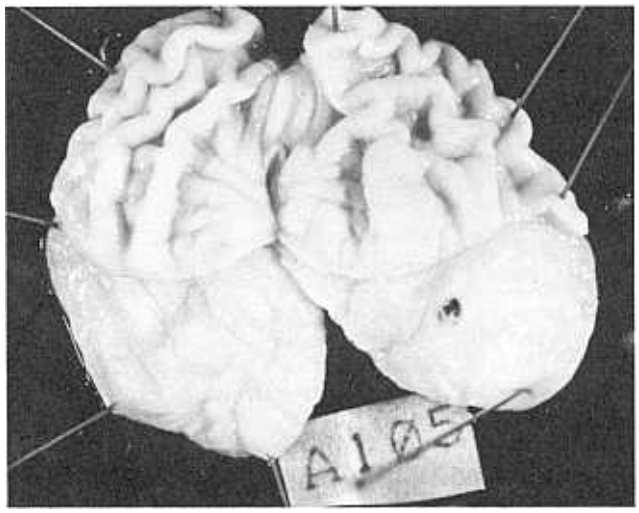

FIG. 2. Photograph of stomach with gastric lesion score = 20.

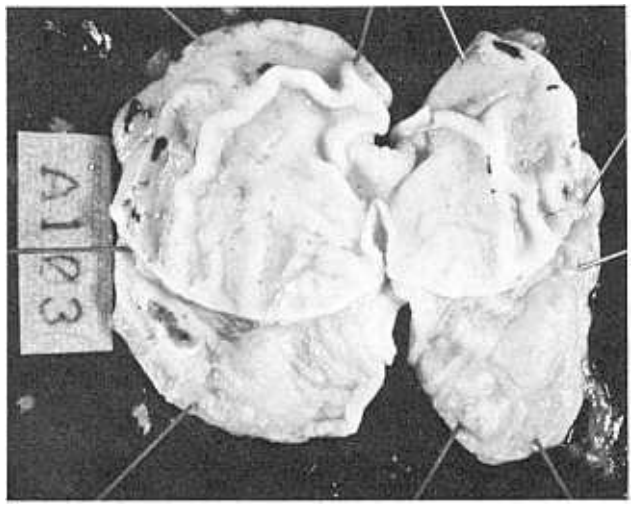

FIG. 3. Photograph of stomach with gastric lesion score = 148.7.

DISCUSSION

The results demonstrate that large lesions involving the lateral hypothalamus which produce aphagia and adipsia also produce greater gastric pathology than that following comparable deprivation or lesions elsewhere. By the fourth day, gastric lesions produced by deprivation, or by a combination of thalamic lesions and deprivation, are sufficiently severe that differences between them and the LH lesioned group are not statistically reliable. This suggests that LH lesions accelerate the formation of gastric pathology primarily for the first 3 postoperative days.

Although the question of how gastric lesions may affect feeding behavior is presently unanswered, certain information leads us to speculate that some forms of gastric pathology may inhibit eating. Routtenberg [24,25] has reported that rats fed 1 hr per day and given access to an activity wheel become anorexic and sometimes die, and it was subsequently demonstrated that rats so treated develop ulcers in the glandular portion of the stomach [19]. Rumenal ulcers may be produced by simply depriving normal rats of food for a period of a few days [20], and deprivation of both food and water produced both rumenal and glandular lesions in the present experiment. In both cases, the severity of gastric lesions is a direct function of the number of days of deprivation. Interestingly, data from other sources show clearly that food deprivation leads to anorexia upon refeeding. Spatz and Jones [27] report that many rats food deprived for 5 to 7 days show profound anorexia and terminal starvation upon refeeding. Hamilton [12] starved independent groups of rats for periods ranging from 2 to 10 days. His results show that longer periods of starvation are associated with greater anorexia upon refeeding. Adolph [4] fasted rats for 7 days. Upon refeeding, most rats were anorexic and subsequently died.

These data, taken together, show that feeding abnormalities tend to occur in situations where gastric pathology tends to occur. While no cause-effect relationship can be presently inferred, the possibility is clearly raised that gastric pathology inhibits eating in rats.

Also of concern is the mechanism by which gastric lesions may be produced. French *et al.* [9], in reviewing earlier human case studies points out that lesions in or near the hypothalamus sometimes produce ulcers, presumably due to autonomic imbalance. Electrical stimulation of the LH increases gastric acid output in rats [17], and, in monkeys, acid release following hypothalamic stimulation is delayed following vagomoty [22]. Feldman *et al.* [7] have shown that hypothalamic stimulation produces gastric abnormalities in cats, and they suggest that activation of

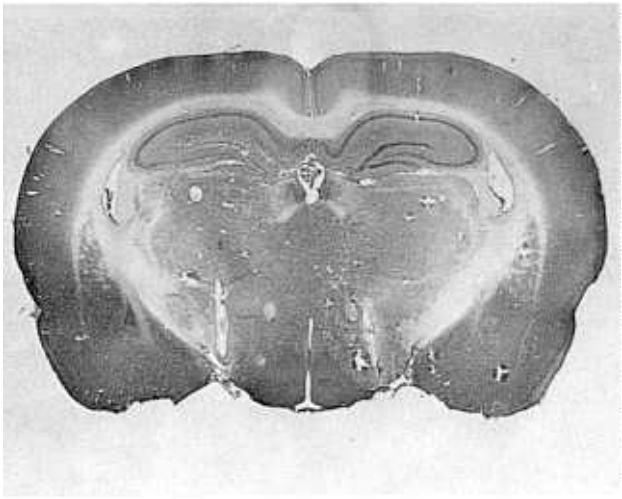

FIG. 4. Photomicrograph of coronal section showing lesion involving the LH. Cresyl violet. The stomach shown in Fig. 2 and this brain section were taken from the same animal.

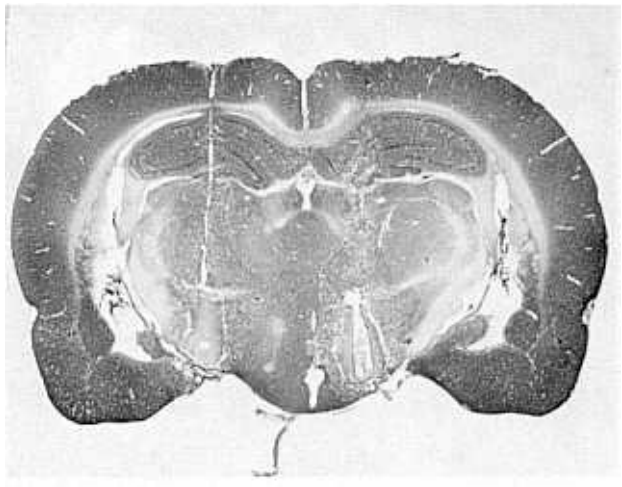

FIG. 5. Photomicrograph of coronal section showing lesion involving the LH. Cresyl violet. The stomach shown in Fig. 3 and this brain section were taken from the same animal.

autonomic centers in the anterior hypothalamus may be responsible. French *et al.* [9] report that ulcers following hypothalamic lesions in cats could be prevented, in some cases, by treatment with vagal blocking agents.

These experiments suggest that hypothalamic lesions produce an autonomic imbalance which in turn produces excessive gastric acid release via the vagus nerves. Additionally, although data on the rat are lacking, experiments with monkeys suggest that the hypothalamus controls gastric acid release via the adrenal glands as well as the vagus [22].

The brain lesions produced in the present experiment were purposely large since we wished initially to effect relatively complete destruction of the LH. In other experiments, currently in progress, we have reduced lesion size and improved bilateral symmetry to more closely approximate the LH lesions described by Powley and Keesey [23]. Interestingly, the gastric pathology produced by this smaller LH lesion is more severe than that presently reported.

More than a decade ago, Teitelbaum and Epstein [29] noted a correspondence of gastric lesions and LH lesions. They report that rats which die 7 to 10 days postlesion often have "... massive ulcers in the stomach and hemorrhages on both stomach and cecum." (p. 76). Similarly, one rat which was repeatedly brain lesioned and recovered died on the fourth recovery because of "... a fatal gastric hemorrhage." (p.86). The authors then state that gastric pathology "... does not seem to be the reason they refuse to eat and drink, because in some aphagic and adipsic animals there has been no macroscopic evidence of gastrointestinal pathology." (p. 76–77).

This last statement is difficult to reconcile with the present observations as well as those of Pare and Temple [20] who showed that simple food deprivation produces gastric lesions. Clearly, aphagic and adipsic rats should develop gastric lesions since, if for no other reason, they neither eat nor drink. Additionally, since the present results demonstrate that LH lesions accelerate the development of gastric pathology, it appears that the role of gastric lesions in the LH syndrome deserves further study.

REFERENCES

1. Ader, R. Plasma pepsinogen level as a predictor of susceptibility to gastric erosions in the rat. *Psychosom. Med.* **25**: 221–232, 1963.
2. Ader, R. Effects of early experience and differential housing on behavior and susceptibility to gastric erosions in the rat. *J. comp. physiol. Psychol.* **60**: 233–238, 1965.
3. Ader, R., R. Tatum and C. C. Beels. Age of separation from the mother and susceptibility to gastric ulcers in the rat. *J. comp. physiol. Psychol.* **53**: 446–454, 1960.
4. Adolph, E. F. Urges to eat and drink in rats. *Am. J. Physiol.* **151**: 110–125, 1947.
5. Braun, J. Jay. Neocortex and feeding behavior in the rat. Paper presented at the 12th annual meeting of the Psychonomic Society, St. Louis, 1971.
6. Epstein, A. N. The lateral hypothalamic syndrome. In: *Progress in Physiological Psychology.* Vol. 4, edited by E. Stellar and James Sprague. New York: Academic Press, 1971, pp. 263–317.
7. Feldman, S., A. J. Behar and D. Birnbaum. Gastric lesions following hypothalamic stimulation. *Archs Neurol.* **4**: 308–317, 1961.
8. Freimark, S. J. Effects of electrical stimulation of the brain on the formation of acute gastric lesions. *Physiol. Behav.* **11**: 855–859, 1973.
9. French, J. D., R. W. Porter, F. K. von Amerongen and R. B. Raney. Gastrointestinal hemorrhage and ulceration associated with intracranial lesions. *Surgery* **32**: 395–407, 1952.
10. Gold, R. M. Aphagia and adipsia following unilateral and bilaterally asymmetrical lesions in rats. *Physiol. Behav.* **2**: 211–220, 1967.

11. Grossman, S. P. and L. Grossman. Persisting deficits in rats "recovered" from transections of fibers which enter or leave hypothalamus laterally. *J. comp. physiol. Psychol.* **85**: 515–527, 1973.
12. Hamilton, C. L. Problems of refeeding after starvation in the rat. *Ann. N. Y. Acad. Sci.* **157**: 1004–1017, 1969.
13. Hamilton, L. W. and F. A. Katske. Rapid gastric ulceration in a modified shuttlebox. *Physiol. Psychol.* **1**: 188–190, 1973.
14. König, J. F. R. and R. A. Klippel. *The Rat Brain.* New York: Krieger, 1970.
15. Luparello, T. J. Restraint and hypothalamic lesions in the production of gastroduodenal erosions in the guinea pig. *J. Psychosom. Res.* **10**: 251–254, 1967.
16. Luparello, T. J. Neurogenic gastroduodenal erosions in the guinea pig. *J. Psychosom. Res.* **11**: 299–306, 1967.
17. Misher, A. and F. P. Brooks. Electrical stimulation of the hypothalamus and gastric secretion in the albino rat. *Am. J. Physiol.* **211**: 403–406, 1966.
18. Morgane, P. J. Medial forebrain bundle and "feeding centers" of the hypothalamus. *J. comp. Neurol.* **117**: 1–25, 1961.
19. Pare, W. P. and V. P. Houser. Activity and food restriction effects on gastric glandular lesions in the rat: the activity-stress ulcer. *Bull. Psychon. Soc.* **2**: 213–214, 1973.
20. Pare, W. P. and L. F. Temple. Food deprivation, shock stress, and stomach lesions in the rat. *Physiol. Behav.* **11**: 371–375, 1973.
21. Parker, S. W. and S. M. Feldman. Effects of mesencephalic lesions on feeding behavior in rats. *Expl Neurol.* **17**: 313–326, 1967.
22. Porter, R. W., H. J. Movius and J. D. French. Hypothalamic influences on hydrochloric acid secretion of the stomach. *Surgery* **33**: 875–880, 1953.
23. Powley, T. L. and R. E. Keesey. Relationship of body weight to the lateral hypothalamic feeding syndrome. *J. comp. physiol. Psychol.* **70**: 25–36, 1970.
24. Routtenberg, A. "Self-starvation" of rats in activity wheels: adaptation effects. *J. comp. physiol. Psychol.* **66**: 234–238, 1968.
25. Routtenberg, A. and A. W. Kuznesof. Self-starvation of rats living in activity wheels on a restricted feeding schedule. *J. comp. physiol. Psychol.* **64**: 414–421, 1967.
26. Seigel, S. *Nonparametric Statistics.* New York: McGraw Hill, 1956.
27. Spatz, C. and S. D. Jones. Starvation anorexia as an explanation of "self-starvation" of rats living in activity wheels. *J. comp. physiol. Psychol.* **77**: 313–317, 1971.
28. Stevenson, J. A. F. and D. G. Montemurro. Loss of weight and metabolic rate of rats with lesions in the medial and lateral hypothalamus. *Nature* **198**: 92, 1963.
29. Teitelbaum, P. and A. N. Epstein. The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. *Psychol. Rev.* **69**: 74–90, 1962.