STRESSOR EXPOSURE AND HUMAN INTERFERON PRODUCTION

by

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INTRODUCTION

Exposing mice to stressors considered psychosocial can alter their
resistance to infections, e.g. to polio, herpes simplex, coxsackie
and polyoma viruses (for a review see 1). It has been hypothesized that
man's susceptibility to infections may be increased by exposure to
psychosocial stressors (2, 3). The endocrine and immunological mechanisms
involved are believed to be complex. Changes in the interferon system,
which is known to play a part in the anti-viral defence process, have
been reported in animals exposed to psychosocial stressors. Interferon
levels fell transiently when mouse interferon procuction was stimulated
<u>during</u> a stressor exposure (4, 5) but the interferon titer did not change
at other timing schedules. Mouse interferon formation was enhanced, on
the other hand, when stimulation took place five hours <u>after</u> stressor
exposure (6). As these studies were concerned with whole-body inter-
feron production, it is conceivable that the results could be accounted
for, at least in part, by changes in the cell quantities producing the
interferon. Nothing is known about the human interferon system's sus-
ceptibility to psychosocial stimuli. This report concerns a study of
stressor exposure in man where the ability of circulating lymphocytes
to produce interferon was measured before, during and after the exposure
and related to concomitant endocrine reactions.

MATERIAL AND METHODS

The subjects were eight healthy female volunteers (informed consent)
aged 23-44 years, mean 33. The experiment, a vigil, started on a
Tuesday morning and ended 77 hours later, on a Friday afternoon. Control
periods were superimposed the day before the start and five days after
the end of the exposure proper. During the vigil, the subjects were
exposed to environmental stressors. The procedure included performance
on a specially designed shooting-range, "firing" an electronic rifle at
small targets (tanks) fitted with photo diodes. An authentic battle noise

from a tape recorder was amplified to a level of 95 dB-C. After an
unabated 2 3/4 hours of such military activity and exposure, there
followed a concentrated 15-minute period for answering questionnaires,
ingestion of standard meals, voiding urine for analysis and attendance
to other toilet functions. In this way the experiment was continued for
three days without any rest or sleep. No activity but the experimental
one was allowed. The subjects were required to sit on their chairs all
the time except when voiding or giving blood samples for analysis. No
stimulants or smoking were allowed. During the control periods the same
standardized procedure was followed except for the experimental stimuli.
Details of the experimental design have been described earlier (7).
Blood samples were obtained the day before the experiment, on the second
day of the vigil, on its last day and five days after the end of the
stressor exposure, always on the same hour of the day.

Interferon production was induced in the blood samples by adding 100
hemagglutination units of Sendai virus per ml as described previously(8).
After incubation for 24 hours at 37°C in a roller, the sera were
separated, dialyzed against pH2 and assayed for interferon by the VSV
plaque reduction method(9). Titers were expressed in terms of the unit
assigned to the standard research preparation 69/19 (International
Symposium on Standardization of Interferon and Interferon Inducers,
London, 1969) and given per ml of serum. The number of interferon units
obtained was related to the number of lymphocytes present in the blood
samples. The results would have been essentially the same even if the
calculations had included the polymorphonuclear cells.

Serum T_4-iodine levels were determined according to a routine procedure
(10) and serum cortisol as described by Laurell(11). The urinary output
of adrenaline and noradrenaline was established according to the method
of Andersson et al. (12). Total leukocyte and differential counts were
made by standard procedures.

EXPERIMENTAL FINDINGS

As this is a pilot study, comprising data from only 8 subjects, the results should be evaluated with caution. Changes represent trends only. The findings should be regarded, not as conclusive evidence, but as a basis for further hypotheses and research on a larger scale.

The interferon-producing ability of the blood samples rose in absolute values during and after the vigil (Fig. 1a). The increase in interferon production per lymphocyte (Fig. 1b) was even more marked.

T_4-iodine and cortisol values are presented in Table 1. The excretion of adrenaline and noradrenaline in urine samples collected between 8.00 and 11.00 a.m. was higher during exposure than during the post-exposure control day (Table 1). The lymphocyte counts exhibited a small decrease during and after the vigil (Table 1).

DISCUSSION

Animal experiments on interferon production in response to psychosocial stimuli have concerned relatively short periods (1). The exposure to mental stimuli has usually lasted only a few hours, though it has been repeated in some experiments. As most stimuli of this type to which man is exposed in everyday life are of considerably longer duration, an experimental design permitting exposure for several days would be closer to real-life conditions. The exposure provoked psychoendocrine arousal, as evidenced by urinary and serum hormonal changes clearly compatible with a stress reaction. The relatively high cortisol levels and the rise in thyroid hormone most probably reflect an increased activity of the neuro-endocrine pathway (7,13). The increased urinary output of catecholamines also accords with previous investigations showing a significant positive correlation with distress scores (7). Hence, the psychosocial stimulus must be considered to have been adequate for the present study.

Attempts have been made to correlate the hormonal changes evoked by the psychosocial stimulation of animals with a synchronous change in interferon production. Solomon et al. (6) hypothesized that the adrenal cortical activity during a stressor exposure may "exhaust" the adrenal cortex, leading to increased interferon production after the exposure. They also compared the enhanced post-stress interferon production with the increased production seen in adrenalectomized mice. In the present study, the highest interferon production (well above the pre-stress values, which were within the normal range) was observed when serum cortisol had returned to the basic level after the vigil. As time spacing differs between the two studies, it is only possible to conclude that both the animal and the human studies reveal an increased propensity of the organism, or part of it, to react with augmented interferon production after stressor exposure.

Studies on the influence of vasoactive amines on the elaboration of interferon in mice (14) showed that the interferon response fell after high doses of epinephrine, whereas low doses of the same hormone caused an increased response. The lowered response could be counteracted with alpha-adrenergic blocking agents. In the present investigation, the rise in interferon-producing ability during the vigil could not be attributed to an increased sympathetic activity, because the interferon levels were highest on the post-stress control day, when catecholamine excretion seemed to be lowest.

In the present study, interferon production was measured only under in vitro conditions and only one viral type and tissue was used for interferon formation. Obviously, it cannot be claimed that the findings have direct clinical implications. It can be suggested, however, that even in man, psychosocial stimuli may affect the ability of certain cells to produce interferon, and, hence, that stress, too, may play a part in the complex defence system against viral infections.

SUMMARY

Exposure of 8 healthy human females to a moderately stressful 77-hour vigil under strictly controlled conditions was accompanied by hormonal changes compatible with a stress reaction. Interferon production was induced by adding Sendai virus to blood samples. The ability of the blood cells to produce interferon rose during the stressor exposure and was highest after this.

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Table 1 a and 1 b

Serum T_4-iodine and cortison values and peripheral lymphocyte counts (1 a) and urinary excretion of adrenaline and noradrenaline collected between 08 and 11 a.m. (1 b).
Means and standard errors of means.

Table 1 a

Variable	Before	2nd day	4th day	After
S-T_4-iodine mg/100 ml	$3,9 \pm 0,3$	$4,5 \pm 0,5$	$5,6 \pm 0,3$	$3,9 \pm 0,2$
S-cortisol mg/100 ml	$17,1 \pm 2,4$	$15,3 \pm 2,5$	$12,0 \pm 1,1$	$8,8 \pm 0,6$
B -peripheral lymphocyte counts x 10^9/l	$3,4 \pm 0,3$	$3,0 \pm 0,2$	$3,2 \pm 0,4$	$2,8 \pm 0,3$

Table 1 b

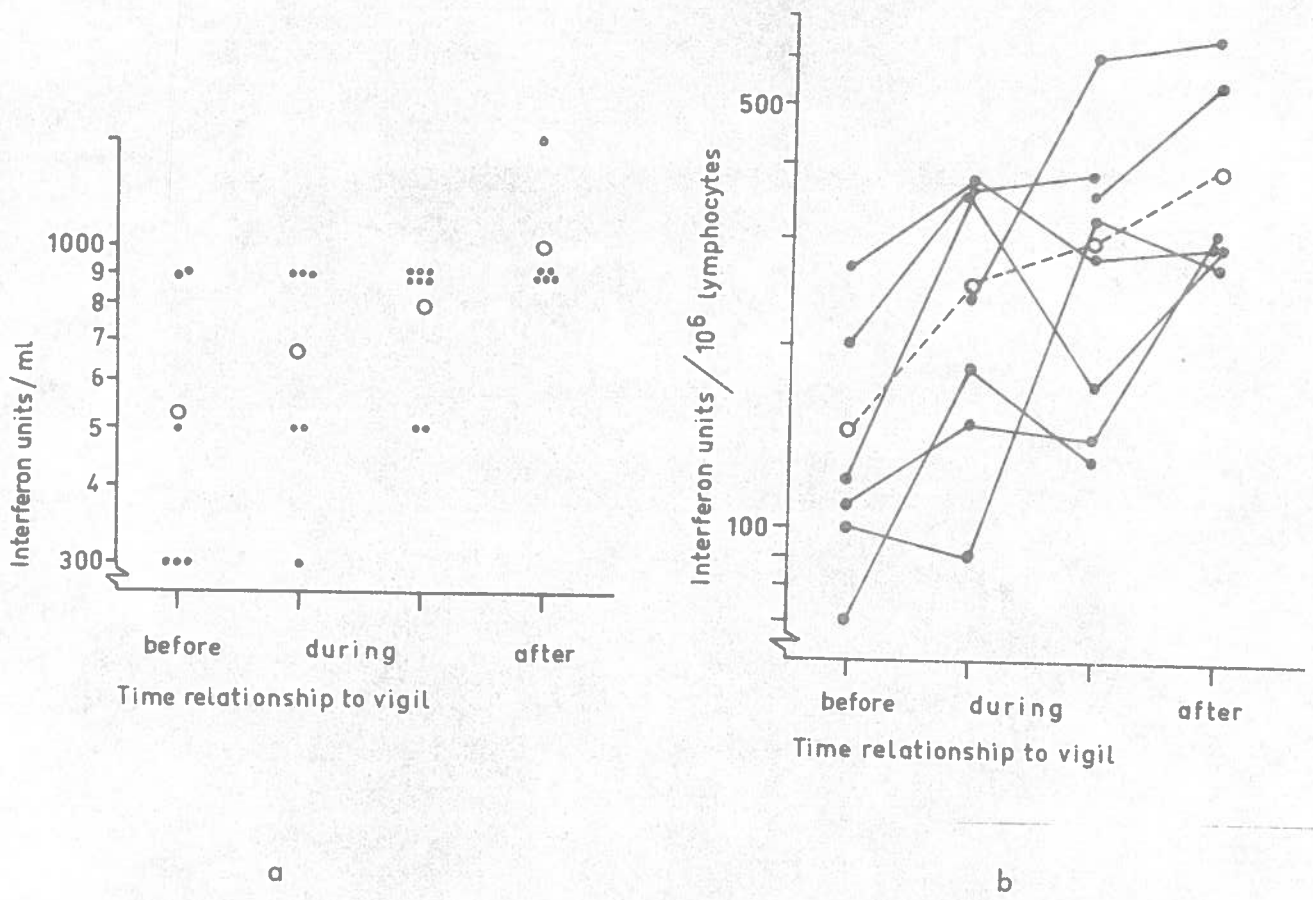|	1st day	2nd day	3rd day	4th day	After
U-adrenaline ng/min	$4,3 \pm 0,5$	$6,5 \pm 0,9$	$7,6 \pm 1,5$	$4,7 \pm 1,3$	$4,3 \pm 0,9$
U-noradrenaline ng/min	$26,9 \pm 1,7$	$31,3 \pm 2,9$	$41,5 \pm 1,3$	$33,6 \pm 2,1$	$27,2 \pm 4,9$

Figure 1.   Total interferon producing ability per ml blood (a)
            and per 10^6 lymphocytes (b) before, during and after
            stressor exposure. Open rings indicate mean values.

CIRCADIAN RHYTHMS IN CATECHOLAMINE

EXCRETION, PERFORMANCE AND

SELFRATINGS

by

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PERFORMANCE AND SELFRATINGS

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Napoleon is said to have used the expression
'two-in-the-morning-courage' to indicate that
deeds of bravery should not be expected from
a soldier at that hour.

INTRODUCTION

The problem

The occurrence of circadian rhythms has been demonstrated in several
measures of physiological arousal. It has been assumed that a circa-
dian "clock" governing these rhythms may be sited in the reticular
formation of the midbrain (Halberg, 1962, Mills, 1966). The reticular
formation has been regarded as a general activation or arousal regula-
ting center. Much research has been devoted to the establishment of
relationships between physiological arousal on the one hand and
measures of wakefulness and performance on the other. This has been
done chiefly by using environmental stimulation to evoke psycho-physio-
logical reactions. Against this background there is reason to study
the relationships between these sets of parameters in the context of
circadian rhythms. Associations may be hypothesized between circadian
rhythm parameters in measures of physiological arousal and in measures
of performance and "subjective arousal".

Earlier studies

Adrenaline excretion has been regarded as a sensitive measure of
general arousal and has been shown to correlate with performance and
selfrated arousal (cf. Frankenhaeuser, 1970). Urinary adrenaline ex-
cretion, as well as noradrenaline excretion, were shown by Euler et al.
(1955) to be lower at night than during the day. Studies in the last
few years have demonstrated circadian rhythms in both hormones. Thus,

Aschoff et al. (1972) reported on 6 subjects living in an underground chamber, and exposed to an artificial light-dark cycle (sleep and darkness between 2330 and 0730); urine samples were collected every 3 hours during 4 days. There was no analysis of rhythm parameters but total urinary catecholamine excretion had an apparent maximum in the afternoon and a minimum in the small hours. Reinberg, Halberg, Ghata, Gervais, Abulker, Dupont & Caudeau (1969) performed cosinor analysis (fitting of cosine functions) on data collected during habitual diurnal activity and during bed rest (with ordinary night sleep), with a hypocaloric diet in both conditions; they obtained estimated phases of between about 12 and 15 hours for the urinary excretion of adrenaline as well as noradrenaline. In a study of four days sleep deprivation, Fiorica, Higgins, Lampeter, Livegola, & Dawis (1968) obtained a flattened circadian curve for the urinary excretion of total catecholamines, with a heightened overall level after the first sleepless night and a less pronounced nightly minimum in the sleep deprived group as compared to an undeprived control group. The curve of the control group was very similar from day to day, with high values in the daytime (06-18 hours) and a marked minimum at 02-06 hours.

Since Kleitman (1939) demonstrated that measures of performance display circadian variation, a relatively large number of studies have emerged in this field. On the whole, performance has been shown to be lowest at night and highest during the day (cf. Colquhoun, 1971).

Some studies of circadian performance rhythms during sleep deprivation have shown that the cycle tends to be more pronounced than under normal sleep conditions (Loveland & Williams, 1963; Drucker et al., 1969). Alluisi & Chiles (1967) even found that sleep loss elicited circadian rhythms that had not been apparent before the vigil.

In a systematic series of studies by Aschoff, Giedke, Pöppel, and
Wever (1972), the loss of one night's sleep did not change performance
rhythms when subjects were studied in isolation, whereas with a group
setting it eliminated the nightly minimum; in a third experiment, with
two groups of three subjects each and the loss of two nights' sleep,
performance deteriorated and the rhythm became irregular.

Subjective arousal has also been shown to vary circadianly. Dermer &
Berscheid (1972) noted high arousal ratings during the day, with local
maxima at about 13 and 20 hours, and a marked minimum around 05 hours.
Fort & Mills (1972), using Thayer's AD-ACL, obtained a minimum for
subjective "activation" around 04-06 hours and a high level during the
day and evening.

A relationship between circadian rhythms in physiologic variables and
wakefulness was suggested originally by Kleitman (1939, revised 1963).
More recently, Murray, Williams & Lubin (1958), in a study involving
98 hours of sleep deprivation, concluded that body temperature and
fatigue ratings are negatively correlated. Schubert (1969) found a
positive correlation between performance in a psychomotor task, and
body temperature and heart rate, when measured over waking hours, and
concluded that "simple task rate is a direct function of diurnal
sympathetic predominance". Several other authors have claimed that
the diurnal rhythm of performance is parallelled closely by that of
body temperature (Blake, 1967, Loveland & Williams, 1963, Jansen & al.,
1966, Colquhoun & al., 1968a and b). Aschoff et al. (1967), however,
questioned the existence of a direct connection between temperature
and wakefulness and observed that the phase relationship between the
two was altered in subjects isolated in underground bunkers. They
suggested instead that there may be two separate oscillators.

Purpose of the present study

As indicated above, circadian variations have been found in adrenaline excretion as well as in performance and subjective arousal. No study, however, has yet been reported in which all three aspects of arousal - physiological, subjective and behavioural - have been measured simultaneously.

We have studied - in a series of experiments designed to test the ability of military personnel to endure a three-day vigil under conditions of continuous activity and a "stressful" milieu - circadian rhythms in catecholamine excretion, performance and "subjective arousal". The present paper is concerned with two experiments, in which a total of 29 subjects were deprived of sleep for 72 hours with 3-hourly measurements of urinary catecholamines, self-ratings, and performance. Preliminary reports have been published by Fröberg, Karlsson, Levi & Lidberg (1972a) and Fröberg et al. (1972b). Other aspects of these studies have been reported by Levi (1972).

The purpose of this study was to answer the following questions:

(1) Are there psychophysiologic circadian rhythms which persist under conditions of sleep deprivation with continuous activity and regularly spaced meals?

(2) If so, what are their characteristics in terms of the shape of the curves, phases and amplitudes?

(3) What time relationships exist between different functions, i.e. physiologic, subjective and performance measures?

METHODS

The subjects were originally 32 officers and corporals (age range 20-44, mean age 29) but three had to be discarded because of incomplete data. Thirteen of the remaining subjects participated in Experiment I and 16 in Experiment II. They volunteered to participate, were all in full health and either non-smokers or had agreed to give up smoking for the duration of the experiment.

During the day prior to the experiment proper the subjects went through a medical examination and were given some practice on the shooting task. Both experiments started on a Tuesday morning and ended on a Friday afternoon, 75 hours later. At the beginning of each 3-hour period the subjects emptied their bladders, drank 300 ml of tap water and were served two sandwiches (always of the same type). While eating, they completed a rating form which included ratings of how "fatigued" and "stressed" they had felt during the last three hours. Ratings were made by the method of ratio estimation (cf. Frankenhaeuser et al., 1967). This procedure was repeated every three hours throughout the experiments, i.e. 25 times.

The experiments started with a three-hour control period during which the subjects listened to soft music and read magazines. For half of the subjects of each experiment this period occurred at 0800-1100 hours (subgroups 1 and 3), for the other half (subgroups 2 and 4) at 1100-1400 hours. During the subsequent 72 hours, divided into 24 three-hour periods, they were exposed to conditions as follows. The procedure included performance on a shooting range, "firing" an electronic rifle at small moving targets containing photo-diodes. The numbers of shots and hits were registered every three hours, and the results were reported to the subjects. During alternate periods pendant lamps were

lit, while in the intervening periods the only illumination came from weak footlights near the target area. In the latter periods, moreover, the subjects were exposed to a taperecorded battle noise (maximum 95 dB-C).

After 2 3/4 hours of the activity described above, there followed a concentrated 15 min period for answering questionnaires, ingestion of a standard meal as described above, voiding urine for analysis of adrenaline and noradrenaline (Euler & Lishajko, 1961) and attending other toilet functions. The physical setting was such that the shooting task was performed in a large room with all subjects seated in a row facing the range.

No activity but the experimental one and no stimulants were allowed. The subjects were required to sit on their chairs at all times except when voiding. They did not see any daylight and were deprived of their watches but were aware of the fact that urine voiding occurred every three hours.

Analysis of data

The two subgroups - starting the shooting task at 1100 hours (sub-groups 1 and 3) and 1400 hours (subgroups 2 and 4), respectively - of each experiment were treated separately.

The data were analyzed in the following ways:

I. As a first step in the analysis, differences between time points were tested by means of analysis of variance for each 24-hour series. If the difference was significant ($p < .05$), the second step was undertaken.

II. For each subject, variable, and 24-hour period (starting at 1100
hours or 1400 hours, respectively,), cosine functions were fitted
of the form:

$$Y_t = Co + C \cdot \cos (wt + phi)$$

where Co is the level, C the amplitude, w the period (in our case
24 hours), t time and phi the phase.

This was accomplished by means of a computer program based on a
method described by Mills (personal communication). The criterion
for fitting a cosine curve is to minimize the sum of squared de-
viations of the observed data from the theoretical curve. Phase,
amplitude and level were changed iteratively until this state was
reached.

There are no straight-forward methods available for testing the signi-
ficance of a rhythm from short series data (for a discussion of this
and related problems, see Sollberger, 1970). In order to have a basis
for judging the effect of sine fitting, the residual variance was
computed and compared to the between time-points variance.

The output of the program also yielded estimates of mean level (average
of all values for a 24-hour period), amplitude (the distance between
the level and the estimated crest) and phase (the distance from 0000
hours to the time corresponding to the highest point of the fitted
curve) for sample mean series.

RESULTS

Adrenaline and noradrenaline excretion

Time plots of means of all 29 subjects are shown in Figure 1. As may be seen, adrenaline excretion exhibited a circadian rhythm with the highest levels in the afternoon (about 1100 to 1800 hours) and the lowest in the early morning (about 0000 - 0300 hours). Analysis of variance yielded significant differences between time points ($p < .001$) for all four groups and all three days. The results of fitting sine functions to the data are shown in Table 1.

The fits to sine functions were reasonably good in all but one case. At individual level the residual variance (with reference to the sine curve) was lower than that referring to the mean level in all but two cases (N = 87). The phase was estimated to about 1300 - 1500 hours, estimated troughs thus occurring in the small hours (at about 0100 - 0300). The amplitude was around 3 ng/min, which is 40-50 % of the mean level. There was a tendency for both level and amplitude to increase with the duration of sleep deprivation. The estimates of level and amplitude were significantly higher for day 3 than for day 1 (t-tests based on individual estimates for 29 subjects yielded $p < .001$ and $p < .01$, respectively). The shape of the circadian curve was rather similar in the four groups. There were no systematic differences between the periods with noise and reduced light and those without.

Noradrenaline excretion did not exhibit as regular a circadian variation as adrenaline. Analysis of variance showed that only one group had significant differences between time points for all days (Table 2).

The phase was estimated to about 0700 - 0900 hours, i.e. estimated crests occurred a few hours earlier than those of adrenaline excretion. Neither level nor amplitude changed significantly over the three days. There were no systematic differences between the periods with noise and reduced light and those without.

The number of shots per three-hour period was high during the day and low during the night. The differences between time points were significant ($p < .01$ or less) on all but the last day for three of the groups. The phase was estimated to around 1500 to 1900 hours (with the exception of one case, Table 3), i.e. somewhat larger than the phases for adrenaline excretion. The mean levels decreased significantly from day 1 to day 3 (t-test based on individual estimates of level, $p < .01$). The number of shots did not differ systematically between the periods with noise and reduced light and those without.

The curves for number of hits per period were more irregular than those for number of shots. There were significant differences ($p < .01$) between time points in all cases except for the last day in groups 3 and 4.

The number of hits was, however, systematically lower in periods with noise and reduced light, so that this periodicity was imposed upon the circadian rhythm. Taking the alternate periods separately (see Figure 1), a faint circadian variation is seen, with maxima and minima at approximately the same hours as those for the number of shots. No phase or amplitude estimates were made.

The curve of percentage hits was rather irregular and for only a few 24-hr cycles were there significant between-time-point effects.

Fatigue and stress ratings

The fatigue ratings, made every three hours, showed rather clear cir-
cadian rhythms, besides rising steeply over the three days. Analysis
of variance yielded significant differences in all but one case
($p < .01$ or less). In Figure 2, maximum ratings appear to occur around
3 to 6 a.m., minimum about 12 hours later. The estimation of rhythm
parameters by sine fitting gave estimated phases between about 0300
and 0530 hours, i.e. the estimated troughs were in about the same
range as the estimated crests of performance.

The ratings of "stress" also increased over the three days, but there
were no detectable circadian variations in this variable.

Relationships between variables

Maximum performance (number of shots) and minimum fatigue occurred
when adrenaline excretion was high. The estimated crests of adrenaline
excretion generally occurred earliest, followed by performance and
fatigue ratings.

Comparing the individual estimates of phase over all individuals and
24-hour cycles we found the following. Out of 87 comparisons (indivi-
duals x 24-hour cycles) between times of adrenaline crests and
fatigue troughs, 76 were negative ("subjective arousal" troughs
occurring later than the adrenaline crests), 5 equal, and 11 positive.
Four series were not analyzed due to single missing values. The corre-
sponding figures for comparisons between adrenaline and number of shots
were: 70, 14, 1 (and 2). These figures must of course be interpreted
with great caution since many of the individual curves were irregular
and the fit of the sine curves was rather poor.

To permit further comparisons between the circadian rhythm components of the different variables, the following measures were taken.

Since the levels of fatigue ratings and number of shots increased or decreased, respectively, a simple technique described by Sollberger (1970) was used to remove these trends. This analysis assumes that there are linear changes over 24-hour periods. The resulting mean curves (for all 29 subjects) are presented together with the adrenaline curve in Figure 2.

The fatigue curve appears to be almost a mirror image of the adrenaline curve when the progressive decrease has been removed in this way from the former, although there is a tendency towards a difference in phase.

The relationship between performance (number of shots) and adrenaline excretion appears to be somewhat more complex. Thus, performance stays high during most of the first night but tends to follow the adrenaline curve during the second and third days. There is, however, a clear trend towards a phase difference here, the performance minima occurring later than minimum adrenaline excretion.

Sleep deprivation effects at different phases

In the data presented above, some of the dependent variables displayed increasing or decreasing trends in levels (day means) over the three days of sleep deprivation. Adrenaline excretion increased most during daytime (significant increases between 0800 and 1400 hours. in Experiment I and 1100 - 0200 hours in Experiment II, by analysis of variance for each three-hour period over all three days). Performance (number of shots) decreased significantly at all times of day, although the

decrease was mot prominent during the night. Fatigue ratings increased significantly at all times of day but most during daytime.

DISCUSSION

Although the subjects were confined to a room where they did not see any daylight and were deprived of other _Zeitgeber_ as well, the regularity of the measurement periods enabled them to compute and keep track of the time of day. Consequently, the experiments reported here are not comparable with studies on "free-running" circadian rhythms, where subjects are deprived of all known synchronizers.

Circadian arousal rhythms

The first of our initial hypotheses was partly confirmed, in that most of the dependent variables showed a circadian variation. The most regular and reproducible circadian curves were obtained for urinary adrenaline excretion and fatigue ratings.

The mean of the estimated phases for adrenaline excretion was about 1400 hours. This corresponds with the results obtained by Reinberg et al. (1969) for subjects on a habitual daily routine with normal sleep, and those of Aschoff et al. (1972) for total catecholamines. Thus, the circadian rhythms of urinary adrenaline excretion appear to persist in conditions of sleep deprivation and regularly spaced meals and other activities.

The noradrenaline phase, however, in those cases where it could be estimated, was clearly separated from that of adrenaline, the former

being about 0800 hours. This contradicts the results of Reinberg et al. (1969), whose estimated noradrenaline phase was about the same as that for adrenaline. Differences in experimental conditions could of course be responsible for this descrepancy, as well as the fact that different methods were used for the assay of catecholamines.

The rhythms in the performance measures are well in accordance with other findings (cf. review by Colquhoun, 1971), performance being lowest in the early morning and highest in the afternoon.

Subjective arousal (as inferred from selfratings of fatigue) was highest in the afternoon and lowest in the small hours. Dermer & Bersheid (1972) obtained an average estimated phase of 1739 hours in "arousal ratings", which is about one hour later than our estimate of the fatigue trough. They conclude, however, that a better fit to their data yields two local maxima, around 1300 and 1900 hours, respectively. A similar tendency may be found in our fatigue data (see Figure 2, upper diagram), which show local minima at 1100 - 1400 and 1700 - 2000 hours.

Relationships between variables

When considering time relationships between biochemical and psychological variables it is interesting to note that the estimated crests of urinary adrenaline excretion in all groups occurred earlier than those of performance and fatigue ratings. Thus, it appears that there was no immediate temporal relationship between the rhythm of adrenaline excretion on the one hand and performance and selfrated arousal on the other. Further, although the performance level stayed high during the first night, adrenaline excretion and subjective arousal declined in

the same way as during the following night. Here we have a further in-
dication of dissociation between the physiological arousal measure and
performance. The high level of performance during the first night is
attributed to an increased effort by the subjects in order to counter-
act the circadian activation decline that sets in during the evening
and night.

In conclusion, our experiments have shown that adrenaline excretion,
performance and subjective arousal are low during the night and high
during the day even under conditions of sleep deprivation and regular-
ly spaced meals and other activities. Both the physiological and the
psychological arousal rhythms had crests in the small hours. It seems,
however, as if there was a phase difference of a few hours between
the physiological and the psychological circadian rhythms.

S U M M A R Y

Circadian rhythms in urinary catecholamine excretion, performance and
self-ratings were studied in two experiments with a total of 29 sub-
jects who were deprived of sleep for 72 hours. Adrenaline excretion
and fatigue ratings showed the most consistent diurnal variations;
noradrenaline and performance rhythms were more irregular. The average
phase for adrenaline excretion was around 14 hours, for noradrenaline
about 08 hours, for performance 17 hours and for fatigue 05 hours.
Twentyfour hour levels of performance and "subjective arousal" decreased
over the three days of sleep deprivation, while adrenaline excretion
levels increased.

Table 1. Urinary adrenaline excretion: level, amplitude, time relations and variances of 24-hour rhythms. Results from least square fits to 8 consecutive, 3-hourly periods starting at either 1100 hours or 1400 hours.

Group	n	Day	Analysis of variance p	Esti-mated level	Ampli-tude	Phase hr min	Variance referred to: Mean level	Sine curve	% of variance explained by sine curve
1	6	1	<.001	6.21	2.47	1302	4.02	0.39	90
		2	<.001	7.03	2.57	1447	4.97	1.57	68
		3	<.001	7.52	3.64	1414	8.94	1.51	83
2	7	1	<.001	4.99	1.94	1519	3.45	1.79	48
		2	<.001	5.14	2.79	1403	4.82	0.26	95
		3	<.001	6.03	2.91	1422	5.68	0.95	83
3	8	1	<.001	-	-	-	2.69	2.11	22
		2	<.001	8.62	2.92	1347	5.80	0.93	84
		3	<.001	8.84	3.57	1519	8.47	1.76	79
4	8	1	<.001	4.81	1.70	1237	3.19	1.89	41
		2	<.001	7.38	3.49	1435	7.55	0.62	92
		3	<.001	7.47	3.53	1459	7.70	0.80	90
All Groups and Days *				6.88	3.02	1404			

* Computed from sine- and cosine component estimates of all individuals and days.

Table 2. Urinary noradrenaline excretion: results as indicated in Table 1.

Group	n	Day	Analysis of variance p	Estimated level	Amplitude	Phase hr min	Variance referred to: Mean level	Sine curve	% of variance explained by sine curve
1	6	1	.004	19.1	2.6	0913	4.13	0.75	82
		2	.004	20.2	2.3	0743	3.20	0.76	76
		3	.01	21.0	2.3	0744	3.42	0.97	72
2	7	1	.10	-	-	-	-	-	-
		2	.23	-	-	-	-	-	-
		3	.01	16.0	1.2	0754	0.93	0.20	78
3	8	1	.003	24.2	2.8	0717	4.74	0.95	80
		2	<.001	26.9	3.8	0802	-	-	-
		3	.25	-	-	-	-	-	-
4	8	1	.82	-	-	-	-	-	-
		2	.03	-	-	-	4.70	4.03	14
		3	.68	-	-	-	-	-	-
All Groups and Days*	87			22.3	1.75	0816			

*Computed from sine- and cosine component estimates of all individuals and days.

Table 3. Shooting performance - number of shots: results as indicated in Table 1.

Group	n	Day	Analysis of variance p	Estimated level	Amplitude	Phase hr min	Variance referred to: Mean level	Variance referred to: Sine curve	% of variance explained by sine curve
1	6	1	<.001	1239	130	1910	16132	10089	46
		2	.004	764	224	1439	35418	8470	76
		3	<.001	664	262	1540	42707	6174	86
2	7	1	<.001	1289	394	0416	101000	39204	61
		2	<.001	1218	404	1449	97000	4104	96
		3	.08	-	-	-	-	-	-
3	8	1	<.001	1124	153	1841	13182	1976	85
		2	<.001	740	278	1614	48191	9394	81
		3	.79	-	-	-	-	-	-
4	8	1	<.001	1241	220	1717	33357	11480	66
		2	<.001	850	329	1834	64518	13931	78
		3	.54	-	-	-	-	-	-
All Groups and Days	87			941	150	1712			

Table 4. Fatigue ratings: results as indicated in Table 1.

Group	n	Day	Analysis of variance p	Estimated level	Amplitude	Phase hr min	Variance referred to: Mean level	Sine curve	% of variance explained by sine curve
1	6	1	<.001	176	67	0411	3224	1035	68
		2	.01	291	78	0359	3976	871	78
		3	.003	347	59	0530	2155	556	74
2	7	1	<.001	139	23	0351	689	113	84
		2	<.001	175	29	0308	553	103	81
		3	<.001	187	41	0449	937	65	93
3	8	1	.003	145	53	0429	1849	508	73
		2	<.001	203	29	0501	466	45	90
		3	.70	-	-	-	-	-	-
4	8	1	<.001	142	61	0454	2066	225	89
		2	.002	205	45	0519	1117	123	89
		3	.004	228	23	0448	488	298	39
All Groups and Days	87			205	40	0511			
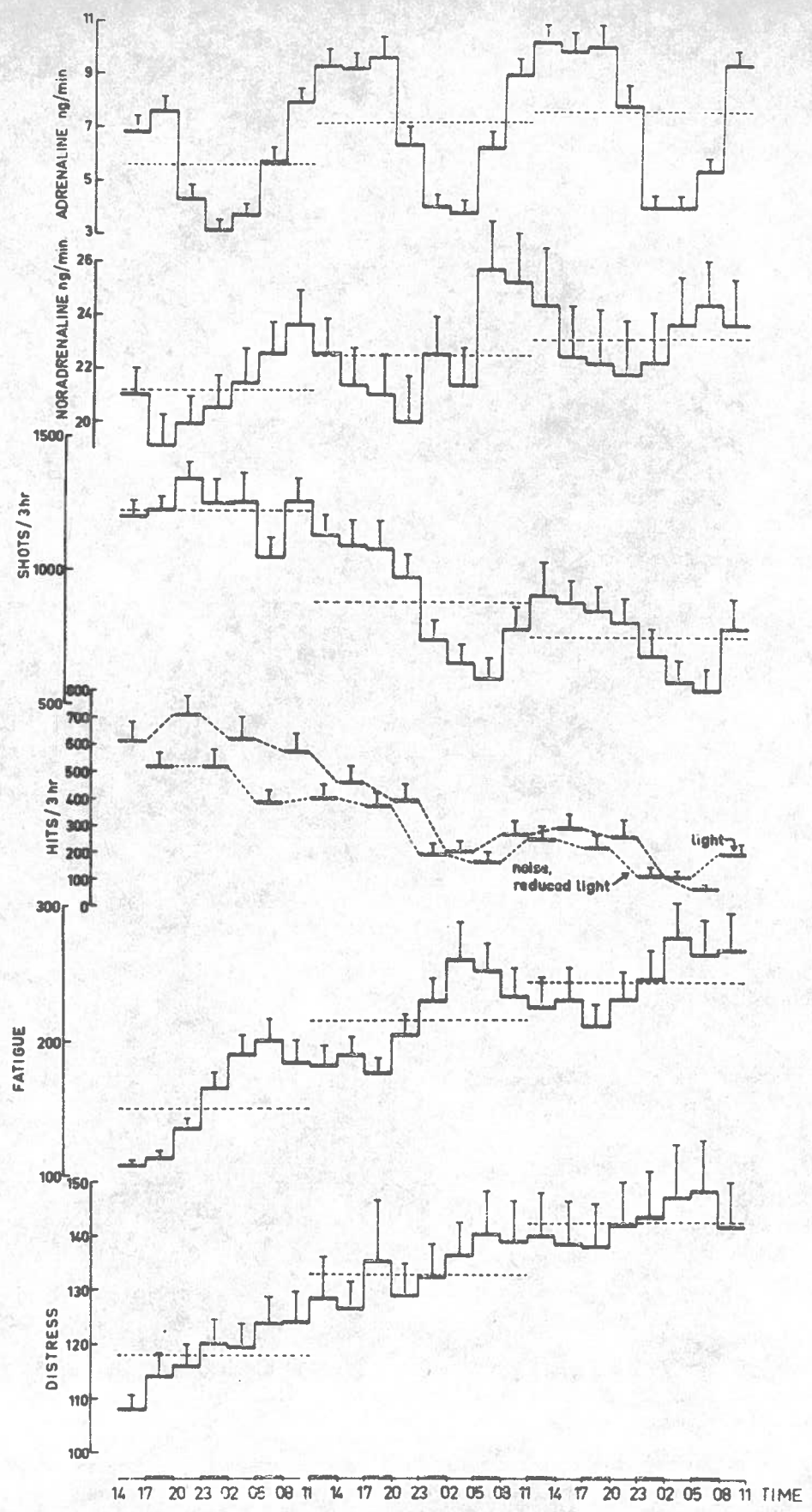
Figure 1. Urinary adrenaline and noradrenaline excretion, number of shots and hits per 3 hours, and fatigue and distress ratings. Means and standard errors for 29 subjects. Dotted lines represent 24-hour mean levels.
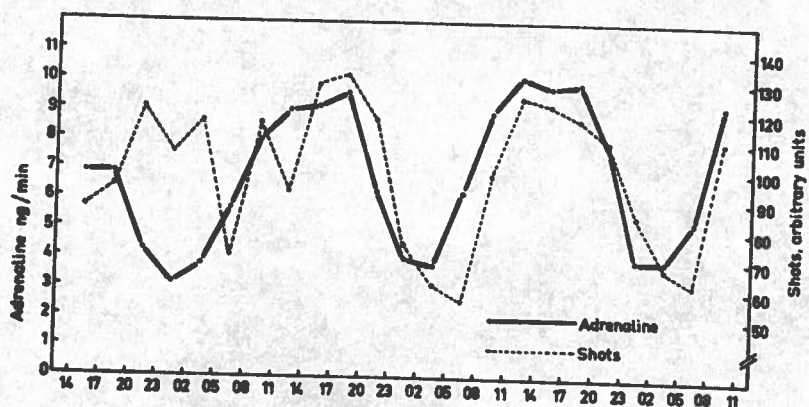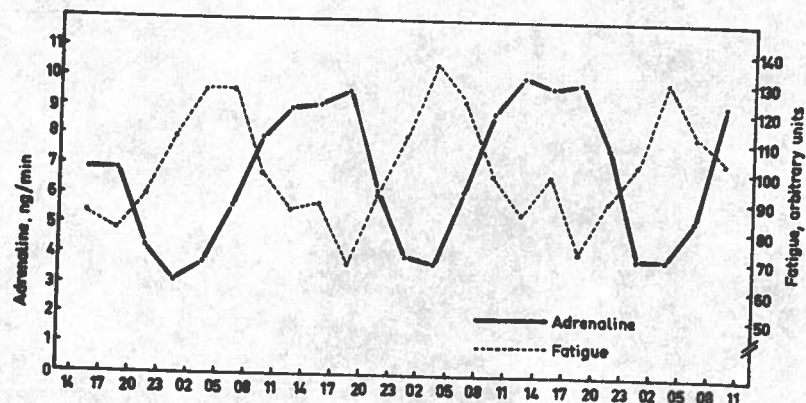
Figure 2. Adrenaline excretion and fatigue ratings (upper diagram) and performance (lower) during 72 hours sleep deprivation. Means for 29 subjects after removal of increasing or decreasing trends in fatigue and performance curves, respectively (see text).

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ETHOLOGY, PSYCHIATRY AND PSYCHOSOMATIC MEDICINE

A review with particular regard to basic
research by the 1973 Nobel Prize laureates:
Karl von Frisch, Konrad Lorenz and Nikolas
Tinbergen

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During the first decades of this century, research into animal behaviour was almost at a dead end. None of the contradictory schools of thought then in fashion proved genuinely fruitful. The vitalists regarded instincts as fundamentally inexplicable, mystical forces inherent in the organism and governing the behaviour of the individual; the reflexologists viewed animal behaviour from a strictly mechanical vantage point and the behaviourists tried to interpret behaviour as the exclusive result of learning. A fruitful way out of this dilemma was found by some researchers who studied the function of the behaviour of different animal species in the struggle for survival. Behaviour thus came to be seen as the result of a process of selection in common with other qualities, anatomic as well as physiological. The 1973 winners of the Nobel prize for physiology or medicine – Karl von Frisch, Konrad Lorenz and Nikolas Tinbergen – occupy a special position among these researchers. They are the main founders of the new science known as "comparative behavioural science" or "ethology" (from ethos, meaning custom or habit). The history of ethology has been described by, among others, J. Huxley (1963) and Eibl-Eibesfeldt (1970). The latter's book, "Ethology – the Biology of Behavior", contains the following passage:

> "The main emphasis of ethological research initially dealt with
> 'the study of instinct' but without being limited to this.
> Ethology is a natural science, a branch of biology, from which it
> took the comparative method for the study of behavioral morphology
> and the analytic method for the causal analysis of behavioral
> physiology. Its philosophical basis is a critical realism. Its
> orientation is neo-Darwinistic and it enjoys a fruitful exchange
> of ideas with other schools of behavior ..."

One could hardly wish for a better definition in brief of the methods and aims of ethology. The aim is to give an objective description of behaviour, of its "morphology", in different animal species, and to draw comparisons. The differences are explained in the spirit of neo-

Darwinism as being due to selection from random variations of genetic origin. Behaviour is regarded as an expression of neurophysiological processes. Ethology is thus a science which studies behaviour from a biological vantage point and therefore considers itself a branch of physiology. Significantly enough, the institution where Konrad Lorenz was working until recently is called the "Max-Planck-Institut für Verhaltensphysiologie".

Karl von Frisch was born in 1886 and can now look back on 65 years of fruitful research. His first studies, dating from about 1910, concerned changes of colour in fish, which he showed to be controlled by the epiphysis, the midbrain and the sympathetic nervous system. Since it had been claimed that fish and invertebrates were colour-blind, he set out to prove this, attempting to train fish to collect food only from signs of a particular colour. It transpired that fish were capable of learning to distinguish between several colours and that their sense of colour was fairly congruent with man's. Later von Frisch went on to study the colour vision of bees by similar methods and found that they can distinguish ultraviolet, as well as yellow, blue and turquoise.

Since 1915 von Frisch's research has been almost entirely concerned with various problems connected with the behaviour of bees. He has become most widely known through his analyses of their way of communicating with each other, their "language". By a very comprehensive series of elegant experiments he has shown that bees employ different "dances" to communicate with each other. When a bee has found flowers with nectar near the hive, it performes a "ring dance" on returning. The bees present in the hive join in the dance, which stimulates them to fly round the hive looking for the nectar. One might say that they have been informed of the presence of nectar nearby. They do not search indiscriminately, only in flowers emitting the scent picked up by the returning dance leader.

He made this discovery in 1919, and in his autobiography (1957) he writes: "Ich traute meine Augen nicht! Sie (the bee that has returned) machte auf der Wabe einen Rundtanz, der die umsitzenden rot betupften Sammlerinnen in helle Aufregung versetzte und sie veranlasste, an den Futterplatz zu fliegen. Das war wohl die folgenreichste Beobachtung meines Lebens."

At an early stage von Frisch noticed that some returning bees performed another kind of dance, which he called by the Tyrolean word "Schwänzel-tanz" (waggle dance). The bee runs forward a short distance and waggles its rear, runs in a semicircle back to where it started, returns along the straight and then back in a semicircle in the opposite direction and so on. It was found that this dance was performed when the bee had found a source of food more than about 50 metres away from the hive. But it took von Frisch until 1944 to find out what the dance meant. He then discovered that in addition to making the bees in the hive look for nectar, it also gave them the distance and bearing. If the dance is performed on a horizontal surface, the alignment of the straight gives a direct bearing on the source of food. In order for the "waggle dance" performed on a horizontal surface to show the right direction, it must take place in such a way that the sun (or at least the sky) is visible. However, bees usually dance inside the hive, where it is dark, and on a vertical honeycomb. And yet the straight line of the dance still con-veys information as to the whereabouts of the food supply in relation to the sun, the direction of the sunlight being translated into that of the force of gravity in such a way that "upwards" means "towards the sun" and so forth. Even when the sun is not visible, bees can still deduce its position by analysing the ultraviolet, polarized light in the sky. They are able to do so thanks to their faceted eyes. Each comprises eight cells and different polarizations of light activate each of these cells to different degrees, so that the activation pattern in the omme-tidium is always different. These discoveries are the result of a host

of very ingenious experiments. Another pecularity is that some sense
of time enables the bees to correct for the movement of the sun. The
distance to the source of food is indicated by the intensity of the
movements of the dancing bee: the more intense its movements, the closer
the target.

Clearly the highly complex "language" of bees is not learned but a
genetically programmed behaviour. Of course von Frisch's discoveries
in this quarter are not directly applicable to mammals, for insects
belong to quite a different branch of evolution. Their behaviour is
seldom if ever homologous, though it is often convergent with that of
the mammals. However, the description of the exceedingly complex
behaviour of bees has prompted an investigation of the adjustment and
information systems of other animal species.

Konrad Lorenz, who was born in 1903, published his first scientific
treatise in 1927 while still a student of medicine. This treatise
concerned behaviour observed by him in halftime jackdaws living in the
attic of his parental home. Since then he has patiently and meticulously
studied the behaviour of a whole series of different animals, mainly
birds of different kinds which have remained at liberty but which he
has tamed to such an extent that they have not been disturbed by his
presence.

Lorenz is above all the systematic observer who has succeeded in
isolating and describing certain important and consistent features
from the bewildering multitude of behavioural traits exhibited by
animals. Of course, this kind of method entails certain risks: the
observer can be suspected of seeing what he expected to see. But a
great many of Lorenz's conclusions have been verified in experimental
studies by him and by other researchers, including Tinbergen. Lorenz
seems, however, to have a very unusual capacity both for observing
animal behaviour and for storing up recollections of it. His research

is essentially concerned with discovery, less with verification, and
in this process free, unconditional observation is an indispensable
first step.

Lorenz's interest centred from the very outset on "instinctive actions",
meaning certain movements performed in a rigid, robot-like manner and
provoked by certain key stimuli (see below). It should be pointed out
that these forms of behaviour are now termed fixed motor patterns
(Erbkoordinationen), "instinctive action" having acquired a wider signi-
ficance. Lorenz showed that in several animal species, when a fixed
motor pattern has been provoked it proceeds "automatically", regardless
of the general situation. It is genetically programmed and once started
is not affected by the situation. Like morphological properties, fixed
motor patterns have developed as a result of evolution, through the
pressure of selection. The closest resemblances between them are also
to be found between closely related species. Lorenz studied motor
patterns of this kind in jackdaws, duck and geese as well as other
species. He showed that a complete instinctive action comprises fixed
motor patterns of this kind together with variable taxes adjusted to
the current situation. This he termed "Instinkt-Dressur-Verschränkung"
("instinct here being used in the former, limited sense of the term).
By choosing a presumably typical (but in fact extremely simple) example,
Lorenz (together with Tinbergen, 1938) was able to analyse this in
detail. When a greylag goose sees an egg outside its nest, it tries to
roll the egg back inside. The movement is absolutely stereotyped: the
egg is caught under the beak and rolled in towards the nest. But the
bird is completely incapable of using its wing or one of its legs to
move the egg - due not to the construction of its extremeties but pre-
sumably to the genetically programmed equipment of the CNS. The movement
cannot be modified if dummies are used - a large cardboard Easter egg
fastens under the bird's "chin" and if the egg is removed after the
rolling process has begun, the movement is continued without the egg.

Whereas this movement towards the body (and the nest) is impossible to modify, correctional sideways movements can be modified - if the egg rocks to one side, this is met with a well-judged movement to return it to the centre. These movements, then, are examples of "taxes".

According to Lorenz, fixed motor patterns are provoked by stimuli particular to each pattern and termed key stimuli. These can be assumed to correspond to a particular organization of the central nervous system, originally termed "das angeborene auslösende Schema", later, at Tinbergen's suggestion, "the innate releasing mechanism" (IRM). This mechanism is assumed to react to key stimuli by prompting or releasing corresponding fixed motor patterns. Lorenz maintains that it is important for key stimuli to be simple and that they must be unlikely to appear haphazardly.

One example is the sea urchin Sphaerechinus, which displays a very complicated flight- and fight reaction in response to a single chemical stimulus secreted by its arch-enemy, the starfish Asterias (Lorenz 1935). This of course is highly practical because it is a sensitive and specific reaction to the presence of the starfish. Another, more complex example is a reaction peculiar to jackdaws which Lorenz discovered by chance. A tame jackdaw (whose accomplishments included preening Lorenz's eyelashes) became extremely aggressive and pecked holes in his hand when he was holding a pair of black bathing trunks. The same thing happened when he held another jackdaw in such a way that it hung from his hand. Closer analysis revealed that this was obviously a practical, innate reaction. Jackdaws will peck at anything or anybody holding something black in such a way that it hangs downwards - in natural surroundings often a predatory animal that has killed a jackdaw. They will also summon other jackdaws to their aid by means of a special call. Jackdaws have no inherent ability to "recognize" particular beasts of prey, unlike e.g. greylag geese (see below); instead they learn by "experience"

after seeing predatory animals catch other jackdaws. Acquired reactions of this kind are plastic and generalized in a completely different way and are not so mechanically bound up with simple key stimuli as the fixed motor patterns (Lorenz, 1954).

The classical method of determining whether a particular form of behaviour is genetically programmed or acquired is to study "inexperienced" or "naive" animals - for instance young birds hatched by artificial means ("deprivation experiments" or "Kaspar Hauser experiments"). The problem here is that no animal is completely devoid of experience even immediately after its birth. There has been a great deal of discussion on this score, but most of the objections have come from doctrinaire theoreticians of learning and have not invalidated Lorenz's conclusions. But they have forced him (and other ethologists) to argue their conclusions more cogently (cf. Lorenz, 1965).

One example of this method is the study of how inexperienced young chicks react to differently shaped dummies resembling the profiles of birds of prey or other, "harmless" birds. These studies originated in the well-known fact that hens conceal themselves when they see the profile of birds of prey and in the observation made by Lorenz's teacher, O. Heinroth, that tame hens were more frightened of birds with short necks than of birds with long necks. Together with Tinbergen, Lorenz was able to show among other things that a bird profile with wings and one short and one long projection only frightened goslings when it was moved in the direction of the short projection, thus representing a bird of prey, not when it was moved in the other direction, representing, say, a goose. This experiment is simple and convincing, basic and often referred to (cf. Lorenz 1939 and picture in Tinbergen 1951).

The threshold for the elicitation of behaviour varies. Thus it depends on varying intensities of need or motivation connected with endochrine

changes and on whether the behaviour has been provoked recently. If the intensity of need rises, the threshold becomes progressively lower, and the stimuli which can provoke it become less and less specific until finally, at a very low threshold, no stimulus at all is needed. This may result in "vacuum activity". Lorenz quotes many examples, some of them highly amusing. For instance, he describes a tame starling which used to sit on the head of a bronze statue in his sitting room looking up at the ceiling. Suddenly it would behave as though it had spotted an insect, fly up, snap at it, return to its place and perform the kind of rapid shaking movements of its beak normally used to kill its prey. It would then swallow several times, its plumage would rise a little and often its body would tremble slightly, for all the world as if it had eaten its fill. It all looked so convincing that on more than one occasion Lorenz climbed onto a chair to look for insects on the ceiling - without ever finding any. He is moved to ask whether the starling was suffering from hallucinations (Lorenz, 1937). Obviously the starling had had no opportunity of catching any insects, whereupon its complex behaviour began without being prompted by any adequate stimulus. Lorenz has also described a humming bird which attached non-existing building materials to a branch with extremely well-coordinated weaving motions (Lorenz and Tinbergen, 1938).

It is quite obvious that the inverse ratio of the intensity of need and threshold value also applies to man. A man with a full stomach is more particular about his food than a man who is starving. A sexually aroused individual will be less exacting in his choice of a partner ("Du siehst, mit diesem Trank im Leibe, /bald Helenen in jedem Weibe") - and nocturnal sexual dreams with orgasm can be interpreted as a species of "vacuum activity". Ploog (1964) has put the same interpretation on certain kinds of sexual behaviour in psychotic patients.

Lorenz (1965) has expressly emphasized that not only instinctive actions but all kinds of learning are based on the genetically programmed equip-

ment of the individual: "the apparatus which makes adaptive modifiability possible is genetically blueprinted itself". Or:"In regard to behavior, the innate is not only what is not learned, but what must be in existence before all individual learning in order to make learning possible". This seems self-evident, but extreme theoreticians of learning have held a contrary opinion.

Lorenz has above all studied a very special form of learning, namely "imprinting". Briefly, imprinting implies that, during a certain short period of its life, a young animal is highly sensitive to a certain type of stimulus which then - but not otherwise - provokes a particular and irreversible behaviour. Lorenz (1935) describes among other things how newly hatched goslings are programmed to follow a moving object, where- upon they rapidly become "imprinted" to follow this and possibly similar objects. Normally the mother is the first moving object the young set eyes on, in which case all is well, but should it see something else first, the gosling will follow it. For instance, a gosling imprinted by Konrad Lorenz will follow him and refuse to follow a goose. Directly or indirectly, imprinting has extremely important effects on the future life of the individual. Among other things, it may direct its sexual behaviour on individuals of the alien species by which it has been imprinted. Lorenz (1927, 1935) describes a female (!) jackdaw which had been imprinted by human beings and on attaining sexual maturity "fell in love" with the family's maid. There are the bizarre examples of a female goose which was brought up together with hens and fell in love with a Rhode Island cockerel, and of a peahen which at an early stage of its life was put in a menagery cage housing turtles and there- after would never pay court to any other species. These are freaks in their way, but highly illustrative. Imprinting had previously been observed by Heinroth, but Lorenz must be given the credit for having carefully studied, analysed and described the phenomenon, which has since been investigated in closer detail by Hess (1958), among others,

and has proved more complicated than Lorenz originally supposed; the effect on subsequent development can vary between different species, it can display a certain reversibility, sexual imprinting can take place at a critical period after imprinting to the mother, and so on. Lorenz himself has pointed this out (1965) and it does not detract from the value of his pioneering work.

In a number of his works (e.g. 1954) Lorenz has studied the forms of behaviour functioning as sign stimuli (social releasers) in communications between individuals of the same species. Animals living in flocks tend particularly to have a comprehensive repertoire of signals, different movements and sounds, which are innate, i.e. genetically programmed expressions of the animal's intentions or "feelings". Equally inherent is the ability to "understand", i.e. to respond to these signals in what for the purposes of the species is a practical way. The signals have the character of fixed motor patterns, they appear automatically and the reaction of other members of the species is equally automatic. One example has already been mentioned: a jackdaw seeing something black ("dead jackdaw") hanging down from something will attack that something, at the same time emitting a special call summoning other jackdaws, who join in attacking the marauder (see Lorenz 1935). Another example is the "vi-vi-vi" call of the young greylag goose (Lorenz is fond of quoting Selma Lagerlöf's "translation":"Here am I, where are you?"). This call summons the mother, who replies with a "gangangangang" call to calm her progeny. This prevents the young from being left alone, which would be deadly dangerous for them.

Sometimes expressive movements can be susceptible of plastic modification, especially in the case of mammals. This would seem to contradict their character of fixed motor patterns, but Lorenz (1951, 1953) maintains, possibly correctly, that the variable mimic expressions that can be observed e.g. in a dog are the result of rival intentions, e.g. a tendency to aggression and a tendency to flight.

One interesting and frequently occurring phenomenon is the phylogenetic "ritualization" of certain signals. Among other things, this implies that a certain form of behaviour can be incorporated in something with a completely new signalling function. It can then also be changed e.g. by exaggerating the movements. One simple example to be found in a number of birds is that of the male feeding the female during "courtship" - the female behaving in various ways like a young bird soliciting food. This infantile behaviour subdues the aggressiveness which the presence of another individual normally provokes and so permits physical approach and copulation. It is presumably common experience that infantile behaviour subdues aggression and performs a certain function in human mating as well. Lorenz (1958) has made a particularly close study of the highly complex, strictly ritualized and specific courtship behaviour of different species. Mention will only be made here of his analysis of inciting behaviour. When a strange male approaches the pair, the female incites her mate to attack the intruder. In certain species she does so by pointing her beak at the intruder - while in other species she points her beak in a stereotyped movement over her shoulder, with only a slight variation according to the position of the intruder. "Inciting" also serves different functions. In some species it does actually result in' the male delivering an attack, while in others it is merely part of the mating ritual and is more than anything else a "profession of love".

Lorenz has taken a great interest in problems of intra-specific aggression, e.g. in "Das Töten von Artgenossen" (1955) and "Das sogenannte Böse" (1963). He observes the practical function of aggression, e.g. the defence of their territory by fish and birds, resulting in a "suitable" diffusion of the species in relation to food supplies. Aggression between members of the same species is very common, but Lorenz maintains that in normal conditions it seldom leads to killing or even to serious injury. The important thing in territorial conflicts is to impress in one way or another. Although the animals attack one another, a certain balance

appears between tendencies to fight and flight, the tendency to fight being strongest in the centre of the territory, the tendency to flight strongest at a distance from the centre. In gregarious animals, both birds and mammals, the group develops an order of precedence first described in 1922 by Schjelderup-Ebbe as the "pecking order" of chickens. This order is often established by certain combats, in the course of which the "defeated" party will adopt a submissive posture (a dog lowers its ears and puts its tail between its legs) and the interesting thing is that this almost invariably prevents the dominant animal from injuring its defeated adversary. Both forms of behaviour are genetically programmed and automatic. The inhibition is most powerful in gregarious animals of prey with "dangerous" teeth and claws, less pronounced in animals which lack such weapons. Once the order of precedence has been established it is maintained almost exclusively by means of harmless threatening behaviour and guarantees a measure of social stability.

Some of Lorenz's pupils (Schleidt, Schleidt & Magg, 1960) have made a very interesting analysis of signals inhibiting aggression in turkeys. They react to any small or medium-sized object which moves near the nest by pecking at it. They do not normally peck their young - but deaf turkeys will peck their young to death. Aggression is only inhibited by the distinctive cheeping of the young, without which the female is unable to recognize them. She will peck at a mute chick but will let a polecat crawl underneath her if the cheep of a turkey chick is played from a loudspeaker. In other words, the cheep is the only key stimulus provoking maternal behaviour.

Lorenz describes various types of gregarious animals, anonymous groups completely devoid of recognition, anonymous groups where group identity is recognized by a special smell, and finally, groups based on individual recognition. In the last-mentioned variety one often finds a clear order of precedence and ceremonies of greeting which, among other

things, denote higher and lower ranks respectively. This is the case,
for instance, in families of greylag geese, where a special "triumphal
call ceremony" takes place which includes averted aggressive gestures
from the individual being greeted and, finally, a "gobble greeting".
Geese in the same family greet one another in this way from the very
outset, but the "triumphal call ceremony" is particularly intense
during mating. In this case aggressiveness forms part of the processes
of mating and group formation, and Lorenz presumes that something
similar also applies to human friendship.

In many of his works Lorenz has tried to draw conclusions from his
ethological studies of animals which can also be applied to human
problems. Attempts of this kind are made in the book on aggression
mentioned above but also in other works such as "Die acht Todsünden
der zivilisierten Menschheit" (1971) (Uebervölkerung, Verwüstung des
Lebensraums; Der Wettlauf mit sich selbst, Wärmetod des Gefühls,
Genetischer Verfall, Abreissen der Tradition, Indokrinierbarkeit, Die
Kernwaffen). Many of his viewpoints offer a great deal of food for
thought. This applies, for instance, to the postulate of a primary
need of aggression in man, cultivated by the pressure of selection.
This would have served a practical purpose at very primitive stages
when human beings lived in small groups defending themselves from
each other. Competition with neighbouring flocks became the most
important factor of selection and "It is hardly surprising that this
resulted in a dangerous over-production of so-called warlike prowess".
This need has survived the advent of weapons which can be used not
merely to kill individuals but to wipe out our entire species. During
the last few years, Lorenz has often been vehemently criticized for his
opinions, and it has to be admitted that his speculations about man
sometimes tend to be rather illfounded speculations. However, the
criticism has too often been unjustly extended to embrace all results
of his research that do not accord with the own ideology.

Nikolaas Tinbergen was born in 1907. One of his greatest merits is that
he has used a series of experiments, often ingenious, to analyse various
problems concerning animal behaviour. Tinbergen has also made success-
ful attempts to quantify behaviour and so obtain a measure of the power
or strength of different stimuli in eliciting specific behaviour. In
his foreword to Tinbergen's book on the herring gull (1956), Lorenz
writes that Tinbergen is both field observer and laboratory scientist
and that, unlike himself, he does not like "keeping animals and bringing
them up but studies them in the wildness of their natural surroundings,
and the wilder the better".

Tinbergen's first studies, in the early thirties, concerned a digger-
wasp, Philantus (Tinbergen, 1958). He analysed its behaviour in detail
and patiently arranged a series of experiments. These insects dig
individual nests where they deposit captured bees to nourish their
larvae, and Tinbergen was able to show that they find their way back
to their nests with the aid of various landmarks. Above all they rely
on their visual sense, learning the landmarks by means of an endo-
genously programmed aerial circuit.

Although Tinbergen has only published one work together with Lorenz
(1938), it is obvious that they have co-operated and influenced each
other. Some of Tinbergen's achievements, therefore, have already been
mentioned in connection with the work done by Lorenz.

Tinbergen's meticulous experimental studies of the various key stimuli
provoking fixed motor patterns and of how they work together are very
interesting and valuable. Different stimuli can provoke the same motor
pattern with different degrees of intensity. One relatively simple
example is the "zigzag dance" of the male stickleback, which is normally
provoked by pregnant females with their swollen bellies and their heads
pointing upwards. Dummy experiments enabled Tinbergen to show that this
behaviour could be provoked by either of these two signals separately -

by a lump of plastecine or a model fish pointing upwards. But a model
fish with a swollen belly and pointing upwards was the most effective.
Particularly elegant is his analysis of the properties of the beak of
the herring gull which encourage its young to solicit food. Underneath,
where the beak is narrow and yellow, there is a contrasting red patch
which the young peck against. By using dummies of different shapes and
colours and with different degrees of contrast he was able to measure
the different degrees of force with which the stimuli prompted the
young to peck.

In a study of the young of the blackbird (Tinbergen & Kuenen, 1939) it
was found that, although they open their beaks and stretch their necks
simultaneously, these two forms of behaviour could be provoked by
different stimuli. During the first ten days the young are blind and
they are stimulated by the shaking of the nest to open their beaks.
At the same time they stretch their necks upwards. This direction is
determined by the force of gravity, as could be shown by centrifuging
the nest. For the first few days after the young have opened their eyes,
the opening of their beaks is provoked visually but the direction in
which they crane their necks is still determined by the force of gravity.
Later still, both the opening of the beak and the craning of the neck
are determined visually. By using a host of different dummies, the
authors managed to carry out an ingenious analysis of the system of key
stimuli which in natural conditions are represented by the head of the
fully grown bird in contrast to its body.

As early as 1937, Koehler & Zagarus discovered that certain dummies can
be more effective than natural stimuli. Tinbergen has studied this
phenomenon more closely. For instance, one can exaggerate the colouring
on the beak of the herring gull, in which case the young will peck
more intensely than when they are confronted by a natural beak. Some
birds prefer exaggeratedly large dummies to their own eggs. By producing

exaggeratedly coloured dummies, Tinbergen et al. were also able to lure male butterflies more efficiently than with genuine female butterflies (cf. Tinbergen 1951, 1958 and Eibl-Eibesfeldt 1970). This phenomenon is of general relevance. As Lorenz (1954) has observed, mankind has utilized the effect of "supernormal stimuli" on a large scale and in a variety of ways. Man uses sweetening agents, refrigeration or the carbonization of drinks etc. to exaggerate what are normally stimulating properties in his food or drink. Clothing or cosmetics are used to exaggerate e.g. certain secondary sexual characteristics such as a slim waist (stays), the shape of the bust (brassière), rounded hips (bustle), red lips, large eyes (eye-liner) and so on. Drugs can also be seen in these terms. This is particularly apparent in the case of hallucinogens: the experiences they give rise to can be so powerful, so intense, so meaningful and valuable to the individual that "normal" experiences thereafter appear mean and banal. But the abuse of central stimulants and of alcohol as well can also be seen in terms of "supernormal stimuli".

Tinbergen's discovery of what are termed displacement activities (1940, 1952) is immensely interesting. These activities have been studied chiefly in birds. In a conflict situation, for instance when the need for fight and the need for flight are of roughly equal strength, birds sometimes neither attack nor flee. Instead they display behaviour which seems inadequate and irrelevant to the situation. For example, a herring gull defending its territory can start to pick grass, an action belonging to its system of nesting behaviour. Displacement activities of this kind can vary considerably in character according to the situation and the species concerned. As a rule they are of exaggerated intensity and often incomplete. Apart from nesting movements, searching for food, sexual movements and sometimes sleep also occur. The last of these is particularly remarkable, for it shows the active nature of sleep. Cleaning movements are very common and have also been observed in primates. Human beings can behave in a similar manner in situations

of stress: they scratch behind their ears, bite their nails, women straighten their hair, and so on. But there is a certain difference: animal displacement movements are nearly always fixed motor patterns, while human displacement movements are automatic but acquired (Lorenz 1951, Tinbergen 1952).

Tinbergen's highly important theory of the hierarchical organization of instincts was first expounded in "The Hierarchical Organization of Nervous Mechanisms Underlying Instinctive Behaviour" (1950). It appears to be an extremely valuable model for ranging individual items of behaviour in a wider context. Briefly this theory implies that the endogenous patterns of action are arranged in a series of programmes, e.g. one for procreation, another for gathering of food and so on. One beautiful example of such a programme is provided by the mating behaviour of the stickleback. First hormonal changes cause "appetitive behaviour", i.e. migration. The stickleback comes to a mating area where it encounters various stimuli provoking a series of behaviours, from territorial defence and nest construction via mating to care of the young. Thus a series of internal or external stimuli lead to various forms of appetitive behaviour and consummatory acts, usually fixed motor patterns. (For a more exhaustive account, see Tinbergen 1951, 1952 and Eibl-Eibesfeldt 1970).

In one of his latest works (1972) Tinbergen, together with his wife, has studied early childhood autism - the grave mental disease appearing in early infancy and usually resulting in permanent mental defects. Other names for the disease are child psychosis and child schizophrenia. Important symptoms include disruptions of emotional contact with adults and other children, acute anxiety in the presence of trivial phenomena and possible mutism and bizarre movements. The authors begin by observing the behaviour of children when they meet strangers - analogously to the observation of animal behaviour, they have noted events during more or less coincidental meetings in super- markets, when visiting families

with children etc. They have observed the situation of conflict which
arises between fear and the need for contact; it can lead to behaviour
which is temporarily reminiscent of that of autistic children. The
authors assume that in certain specially predisposed children, fear
can greatly predominate and can also be provoked by stimuli which
normally have a positive social value. This method of tackling problems
concerning early childhood autism is original and promising. Although
the authors' conclusions regarding preventive measures and treatment
must be considered tentative, for this very reason their work is of
great interest.

Physiological and medical research based on ethological principles.
As has been shown in the above account, Lorenz, Tinbergen and von
Frisch have among other things discovered basic principles governing
the maturity, organization and elicitation of genetically programmed
behaviour. Their research has since been continued by their successors
in the science of comparative study of behaviour or ethology. The
discoveries have been of great importance for the development of physio-
logy and medicine, especially in recent years.

Although each animal species has its own specific repertoire of instincts,
with special fixed motor patterns, innate release mechanisms and taxes,
the principles involved are fundamentally the same. There seems to have
been a certain reluctance to accept that this can also be applied to
so-called higher animals, man included, for the basic discoveries were
made, not in mammals but in insects, fish and birds. It is true that
various fixed motor patterns among the mammals have been superseded
by more plastic, acquired behaviour, particularly among the primates
in connection with the development of the cortex. But this does not
mean that the fixed motor patterns have disappeared: several of them
can still be demonstrated in man.

In children one can observe a series of fixed motor patterns provoked
by simple key stimuli (surveys in Ploog 1964 and Eibl-Eibesfeldt 1970).
Particularly interesting is the baby's smile, which up to the age of
two months is more easily elicited by two well-defined, contrasting
patches on a round or square disc representing a head than e.g. by
a painted face. There must be two patches, but their location is less
important. In the second month of life the two patches become more
effective if they are placed horizontally than if they are placed
vertically. At about four months the child reacts to mouth movements,
but does not distinguish between models and real faces until about the
age of six months (Ahrens, 1953). Blind children react to their mother's
voice by laughing and they direct their eyes towards the source of
sound (Freedman, 1964). Deaf and blind children can also laugh. Adults
display various fixed motor patterns together with acquired behaviour
in complex chains of action.

Ethology has stimulated a series of studies of non-verbal communication
in animals and human beings (see Hinde/Ed./1972). Several human move-
ments of emotional expression are fixed motor patterns and are to a
great extent shared by individuals in different cultures. One example
is the very common movement connected with greeting, comprising a
rapid lifting and lowering of the eyebrows (Eibl-Eibesfeldt 1970, 1972).
The studies made of the phylogenesis of laughing and smiling by com-
paring them with homologous behaviour in other primates (Andrew 1963,
Eibl-Eibesfeldt 1970, van Hooff 1972) are also of great interest. The
human smile seems mostly related to the originally submissive and
subsequently generally non-hostile "silent bared-teeth display" of the
primates, the laugh with their "relaxed open-mouth display", which is
associated with play, especially play involving elements of aggression.

Lorenz himself (1943) has exemplified key stimuli in man by maintaining
that a number of infant characteristics obviously have this function:

they elicit maternal reactions. This applies to the high domed
forehead, the round cheeks, the large eyes, the soft bodily surface
and a certain style of movement. When the same characteristics occur
among animals (and their young) they arouse the same maternal response
and are regarded as "pretty". This is the case e.g. with Boxer puppies
with their short muzzle, large eyes, soft fur and clumsy movements
and with almost equally snubnosed, soft young birds (tits) - but not
with sharp-muzzled greyhounds or long-beaked magpies.

It would be incorrect to suppose that ethology is _solely_ concerned
with "instincts" and "innate" behaviour. Lorenz (1965) has justly
pointed out that genetic programming governs not only fixed motor
patterns but also what can be learned, in what way and during what
period of life. But he has also shown how important it is for animals
to meet adequate stimuli during certain critical periods: otherwise
their behaviour may become irreversibly abnormal. This is particularly
true of "imprinting", but it also applies to other types of environ-
mental influence. Thus animals growing up in isolation can become
highly abnormal (see below).

Interesting deviations of a sexual nature may develop in animals
exposed to inadequate stimuli during critical periods. We have already
seen how animals imprinted by man are liable to direct their sexual
behaviour towards man instead of members of their own species. Another
interesting observation is that young male mallards kept together
without access to females during the period crucial to their sexual
imprinting can subsequently keep together for the rest of their lives
even if there is a good supply of females (Schutz 1965). Of course,
one must be very careful in extrapolating this to human homosexuality,
but it is important to know that homosexual behaviour can thus be
induced by early environmental influences. Observations have also been
made of behaviour resembling fetichism. Thus a cock which had grown up
in isolation regularly mated with a feather on the ground even in the

presence of females (Fabricius, 1971).

In recent years a series of studies have been made of primates, their behaviour being observed on ethological lines either at liberty or in as natural conditions as possible. This has furnished valuable knowledge concerning forms of communication and also concerning the social structures existing within groups of different ape species. There are important similarities but also important differences compared with man - probably too with man's early ancestors. These studies have done a great deal to put human behaviour in its biological context.

The differences between animals and mankind should not be allowed to obscure the similarities. Ethologists are usually the first to warn against jumping to conclusions regarding human behaviour on the strength of studies of the behaviour of animals (e.g. Tinbergen, 1968), but one should also beware of the opposite extreme of refusing to draw any conclusions at all. Opposition to comparisons between animal and human behaviour appears to stem from the same obscure sources as the resistance formerly encountered by Darwin, although prejudice nowadays tends to be dressed up in political rather than religious costume.

Baboons living at large have been studied e.g. by Washburn & de Vore (1961), chimpanzees at liberty by van Lawick-Goodall (1967, 1973). The great importance of such studies is affirmed among others by Washburn & Hamburg (1968), by Hamburg (1970, 1971, 1973) and by Fabricius (1972). Only a few examples can be quoted here. The baboons display a social organization with a strict hierarchy - a senior male predominates and is surrounded by a harem. He is treated with almost devout admiration by the other members of the group. They gladly seek his company and anyone incurring his displeasure will do everything possible to mollify him. The male leader performs a judicial function and restores order in the event of a dispute, often merely by raising his eyebrows. Serious conflicts only occur when the male leader is sick

or lost - but eventually a new baboon becomes leader. The chimpanzees
have a hierarchy but their groups are not permanent and the same
individuals can belong to more than one group. The ties between mother
and child are very strong among all primates. In the case of the
chimpanzees they are also very prolonged, with the young following
their mothers for nine years.

The nature of the mother and child relationship in man, its importance
to child development and to the adjustment of the child later in life
are problems which have formed the subject of a lively discussion
during the past few decades. The studies made by ethologists of pro-
cesses resembling imprinting also occurring among primates have been
of immense importance here. Originally Lorenz (1935) maintained that
imprinting only occurred among birds, but this has since proved un-
tenable unless the term is defined very narrowly. At all events close
ties soon develop between a young primate and its mother or a substi-
tute for the mother. The question is probably one of convergent develop-
ments in birds and mammals rather than homologous behaviour, for their
lines of development diverged as far back as the reptile stage. But
it was the study of imprinting among birds that prompted studies of
mammals. Dogs undergo a critical period roughly between the fourth
and sixth weeks of their lives, when they develop close and lasting
ties either with fellow members of their species or with a human sub-
stitute. Lambs normally follow their mothers (who in turn follow their
mothers and so on) but if they have grown up in visual, auditive and
olfactory contact with a dog (without any physical interaction), they
will then follow the dog even if it bites and maltreats them (see
Bowlby, 1969).

But the most interesting studies are those that have been made of
primates in the past 15 years, above all the many experiments carried
out with rhesus monkeys by H.F. Harlow and coworkers (Harlow 1959,

Harlow & Zimmerman 1959, Harlow 1962, Harlow & Harlow 1966, see also surveys in Bowlby 1969 and Hamburg 1970). In some of Harlow's experiments the young grew up devoid of contact with their mothers or siblings but instead provided with maternal models either made out of steel wire or covered with soft, terry cloth. The young were able to suck milk from a "nipple" on the model. Young monkeys with a wire mother and a cloth mother to choose between showed a marked preference for the latter, even though they obtained milk from the wire model. A cloth mother also gave far more security if the young were shown a new, "menacing" object. If the young monkey only had a wire mother to go to, it curled up in terror in one corner, but if it also had recourse to a cloth mother it fled to her and then ventured out on cautious excursions to investigate the "dangerous" object. Evidently bodily contact is more important than food supply where security is concerned. It is also very interesting to note the experiments in which a cloth mother was made into a malignant, punitive mother. This is done by a bell ringing (conditioned stimulus), whereupon cold air blows out of holes in the cloth mother. Inspite of these two unpleasant sensations (the bell and the cold air) the young monkey clings to the mother model, if anything more intensely than it clings to a "nice" cloth mother. Thus the need for contact is extremely powerful. Even rhesus young who were maltreated by their real mothers displayed a close attachment to them.

Young monkeys which had grown up in more or less complete isolation (sibling contact is also important) later exhibited serious behavioural disturbances when they were put together with other monkeys. They displayed peculiar motor stereotypes, uncontrolled aggressiveness and abnormal sexual behaviour. Males could not even mate with sexually experienced females. Females were able to learn from sexually sophisticated males, but if they became pregnant they behavied abnormally towards their young. Instead of behaving affectionately and protectively towards their progeny like normal mothers, they were indifferent or

aloof and in some cases were actually aggressive and maltreated them. Isolation has also been shown to have similar injurious effects on chimpanzees (Turner et al., 1969). They were refractory to various attempted forms of pharmacological and "psychotherapeutic" treatment.

Hinde (1968, 1971) has made some interesting studies of the consequences of the mothers in a group of rhesus monkeys being removed from their young for six days when the latter are eight months old. The young seem depressed, show little activity, hardly play at all and eat badly. When the mothers return they cling to them more than usual, hesitate to approach unknown objects, are emotionally unstable and often have outbursts of temper. These changes remain for several months after the brief separation; in some cases they were still evident a year later.

In her studies of chimpanzees living at liberty in Tanzania, van Lawick-Goodall (1967, 1973) observed three young chimpanzees (3-4 years old) who lost their mothers. All of them exhibited behaviour which is best described as depression. Only one of them survived for any length of time, probably because he was "adopted" by an older sister.

Spitz (1945, 1946) and several other researchers have shown that serious and perhaps irreversible mental injury occurs among children at orphanages where there is no possibility of establishing a permanent emotional link to a particular person. Mortality is also appreciably higher, although fully acceptable somatic treatment is given.

The research findings concerning the mother and child relationship resulting from ethological studies of animals, especially primates, have greatly influenced child psychology and child psychiatry. This is particularly apparent from Bowlby's (1969, 1973) monumental work "Attachment and Loss", which is a laudable attempt to integrate the

results achieved through psychoanalytical methodology (almost
exclusively retrospective) with those gained through direct observa-
tions of the mother and child relationship in animals and human beings.
Unfortunately only the first of these works has been available, but
on the strength of this alone one can second Mandler's (1973) verdict:
"Bowlby's brilliant synthesis of modern systems analysis, careful
ethological thought, and the resurrection of the most lasting and
profound insights of Freud's, stands as a model of theorizing".

Detailed knowledge of the normal behaviour of animals, of communica-
tions between individuals and of social structures, is essential for
the important research which concerns the possibly morbid effects of
changes to or interventions in their "normal" psychosocial living
conditions. A comprehensive body of research has developed in this
sphere during recent years. A brief survey has been given by Fabricius
(1971). The title of this survey is significant:"Ethological evidence
of genetically determined behaviour patterns, and conflicts between
these patterns and changed environmental conditions".

At the symposium "Parameters of Emotion" held in Stockholm during the
spring of 1973, J.P. Henry outlined a series of investigations in which
ethological methods had been used to arouse different emotions in ani-
mals and study physiological changes connected with them. He describes
the importance of enabling animals to interact in social groups and
of registering their behaviour, their social hierarchy etc. Thus Rose
et al. (1971, 1972) have carried out interesting measurements of
plasmatestosteron in rhesus monkeys. They found a positive correlation
between plasmatestosteron on the one hand and rank and aggressiveness
on the other. The plasma level declined with declining status and
vice versa. On the other hand Sassenrath (1970) found that the adrenal
response to ACTH was higher in the most inferior animals. Von Holst
(1969, 1972) studied behaviour and physiological changes in individuals

of a Tupaja species (the tree shrew) when one of two animals was
defeated but could not retire. There were clear differences both in
behaviour and in appearance, even when the vanquished animal was
separated from the dominant animal by a net. The hairs on its tail
stood on end (sympaticus activation), it crawled apathetically into
a corner, its fur was neglected and the animal screamed when its
victorious adversary approached. After a few days or weeks the defeated
animal went into a coma and died of uremia due to renal insufficiency.
Serious or even fatal somatic changes were thus brought about by
purely psychosocial stimuli, without the animals having to come into
physical contact with each other. If the victor was allowed to attack
the defeated animal, the latter lay still and let itself be bitten.
The bites were not serious and the animal did not bleed, but it might
die after only a few minutes. (In natural conditions the defeated
animal would have fled and the medical consequences would thus have
been avoided).

Lapin and Cherkovich (1971) describe the effect of disrupted social
relationships among baboons. The highest rank in a baboon community
is generally occupied by an elderly male. If such a male is isolated
and put in a cage by himself, he shows signs of anxiety but these
eventually subside. If he is later allowed to see how other baboons
of lower rank (young ones and females) are given food and if - what
is worse still - he is allowed to see another male together with
females, he will display signs of anxiety and fury. Four or five months
in conditions of this kind resulted in what the authors term "consider-
able stable changes in the higher nervous activity which we regard
as neurosis". Somatic diseases also appear: arterial hypertension,
coronary insufficiency and cardiac infarction.

Henry himself and his coworkers have shown in a series of studies
(e.g. 1967, 1972, 1973) that in mouse communities too it is possible
by means of suitable experimental arrangements to produce social

disturbances leading to prolonged arterial hypertension. Among other things he has studied mice raised in complete isolation (like the rhesus monkeys in some of Harlow's experiments) and then allowed them to form communities in specially constructed cages. Unlike normal mouse communities, where a socially stable hierarchy is soon established, this results in a community characterized by social confusion, chronic territorial conflict and an absence of procreation. The animals display elevated blood pressure, hypertrophied adrenals, an increase of adrenal-medullary cathecholamine-synthesizing enzymes and raised plasma-corticosterone levels. After approximately $\frac{1}{2}$ year the animals develop fixed hypertension and arteriosclerosis, with interstitial nephritis and myocardial fibrosis. In a normal mouse colony the dominant animal displays an initial rise in medullary tyrosine hydroxylase and eventually elevated blood pressure, while the subordinate animals have a higher initial plasma corticosterone level and finally a more pronounced adrenal hypertrophy than the dominant animals. In this connection it is interesting to note that Folkow & Rubinstein (1966) were able to produce permanent hypertension in rats when they stimulated the hypothalamus defence area for several hours each day.

Studies of the effect of psychosocial factors in producing hypertension and other cardiovascular diseases in animals are extremely relevant to the questions now being asked concerning the origin of similar conditions in man. The literature on the subject is highly comprehensive and mention will only be made here of the close resemblance of the results of experiments with animals to observations of man. There is a great deal to suggest that prolonged emotional burdens, "stress", are an important factor in the origin of essential arterial hypertension, e.g. in persons who need to assert themselves and fail to do so, and in occupations involving a great deal of responsibility or frequent conflicts (cf. Wolf et al. 1955 and Brod 1971). This problem is also illuminated by a study like Theorell's (1971). Using Rahe's

methodology he found that an accumulation of "life changes" was common during the period immediately preceding a myocardial infarction.

The effect of psychopharmaca is a function not only of the substance itself but also of the characteristics of the individual and of his situation. Ethological methods are therefore also important to psycho-pharmacological research. Chance (1968) expresses this in the following terms: "psychopharmacology ... needs methods appropriate to the description of unrestrained behaviour". He himself describes the effect of a barbiturate on different kinds of social behaviour in the rat in different social conditions. One simple example of the importance of social situation to the effect of a drug is the far stronger effect of amphetamine when it is given to mice in a group who are enabled to interact than when it is administered to isolated mice (Garattini 1969). By addicts, central stimulants are used par preference in groups.

It should be evident from the above summary that many ethological studies of animals are clearly relevant to human medicine, especially with a view to preventive measures. Insufficient stimulus from mother and siblings (or other playmates) can clearly lead to serious injury. Certain psychosocial situations imply such a burden that they obviously induce illness. It is obvious, and many have observed, that life in a modern western society (and in most other societies) is ill-suited to the behavioural programmes with which man is equipped through the pressure of selection in other, far more "primitive" conditions. Our genetic equipment has probably remained virtually unaltered during the past 50,000 years, at the same time as our culture and the circumstances of our life have been changing more and more. This is an interesting and important sphere of research. Together with anthropologists, archaeologists and others, ethologists can help us to construct a picture of our genetically programmed equipment with its forms of behaviour and behaviour potentials - and of what we are definitely not

built for. Many others besides Lorenz have contemplated aggression and its appurtenant problems, e.g. Tinbergen (1968), Russel & Russel (1968) and Fabricius (1971, 1972, 1973). Hamburg (1971) has among other things studied how the accumulation of individuals and contact with strangers induce aggression among apes and men alike. No doubt ethology has important ideas to offer concerning rational proposals for the solution of social problems and problems of mental hygiene. Unfortunately there are probably a series of formidable irrational obstacles to be overcome before it can do so.

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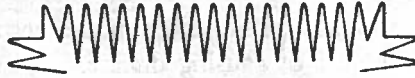
Chapter II

PSYCHOSOCIAL STRESS AND DISEASE: A CONCEPTUAL MODEL

Lennart Levi

OBJECTIVES

THE EVIDENCE that environmental *physical* stimuli may cause physical disease—in the sense that exposure to or avoidance of such stimuli increases or decreases the chance of becoming ill or reverses ill health when it occurs—is established for a large number of environmental factors and diseases.

The role of extrinsic psychosocial stimuli is not so clear. In presenting a survey of present knowledge, we shall consider some hypotheses, speculations and research concerning the relationships between psychosocial stimuli and (1) mechanisms thought to be associated with disease, (2) precursors of disease and (3) disease itself.

In this chapter an attempt will be made to focus on the general *non*specific aspects of man's reaction to a variety of psychosocial stimuli. The author is clearly aware of the theoretical and clinical importance of the stimulus as well as of response *specificity* but feels that the nonspecific aspects are not only equally important but have so far attracted less attention.

DEFINITIONS

First we shall define the terms that represent the basic elements of our conceptual model.[31]

1. *Psychosocial stimuli.* In this context we are referring to stimuli which originate in social relationships or arrangements (i.e. in the environment), affect the organism through the mediation of higher

8

nervous processes, and may be suspected, under certain circumstances and in certain individuals, of causing disease.

2. *Psychobiological program*. This is propensity to react in accordance with a certain pattern, e.g. when solving a problem or adapting to an environment. Determinants of this program in an organism are genetic factors and earlier environmental influences.

3. *Mechanisms*. These are physiological reactions in the organism induced by psychosocial stimuli which, under some conditions of intensity, frequency or duration, and in the presence or absence of certain interacting variables, may lead to precursors of disease, and, eventually, to disease itself.

Stress is used here in the sense that Selye[59, 60] described it, namely the nonspecific response of the body to any demand made upon it; a stereotyped, phylogenetically old adaptation pattern, primarily preparing the organism for physical activity, e.g. fight or flight. These Stone Age responses, which may be provoked by a variety of psychosocial and other conditions of modern life, when no physical action is possible or socially acceptable, have been suspected of eliciting physical and mental distress or malfunction, or even structural damage. Briefly, then, stress is one of the *mechanisms* under certain circumstances suspected of leading to disease.

4. *Precursors of disease*. These are malfunctions in mental or physical systems which have not resulted in disability but which, if continued, will do so.

5. *Disease*. Disease is disability caused by mental or somatic malfunction. Disability is failure in performance of a task. This must always include tasks considered essential, might include tasks considered normal, and, when more is known, will include tasks that are considered optimal. (In applying this definition it is necessary to state the level of the biological hierarchy to which it refers. Disease as defined is different at the cell, organ and organism level.)

6. *Interacting variables*. These are intrinsic or extrinsic factors, mental or physical, which alter the action of "causative" factors at the mechanism, precursor or disease stage. By "alter" we mean they promote or prevent the process that might lead to disease.

Examples to clarify the use of these terms will be given below. It must be said now that although it is often possible to categorize factors according to the above definitions, there are many occasions

when the category is not clear or when categories are interchange-
able. Nevertheless, we think they will facilitate discussion, and prob-
ably lead to a better understanding of the problem.[5,31]

A CONCEPTUAL MODEL FOR PSYCHOSOCIALLY MEDIATED DISEASE AND SOME HYPOTHESES

The combined effect of psychosocial stimuli (1) and the psycho-
biological program (2) determines the psychological and physiologi-
cal reactions (mechanisms (3), for example, stress) of each indi-
vidual. These may, under certain circumstances lead to precursors
of disease (4) and to disease itself (5). This sequence of events can
be promoted or counteracted by interacting variables (6). The se-
quence is not a one-way process but constitutes part of a cybernetic
system with continuous feedback. Our conceptual model[6,13,62] of the
above-mentioned relationships in the pathway of psychosocially medi-
ated disease has been presented in Figure II-1.

Our experimental work has been based on this model and on the
following series of hypotheses. Every psychosocial change can act
as a stressor in Selye's sense of the word. In response to such an ex-
posure, and in accordance with the phylogenetically old adaptation
pattern ("psychobiological program," *cf.* Fig. II-1) which man has
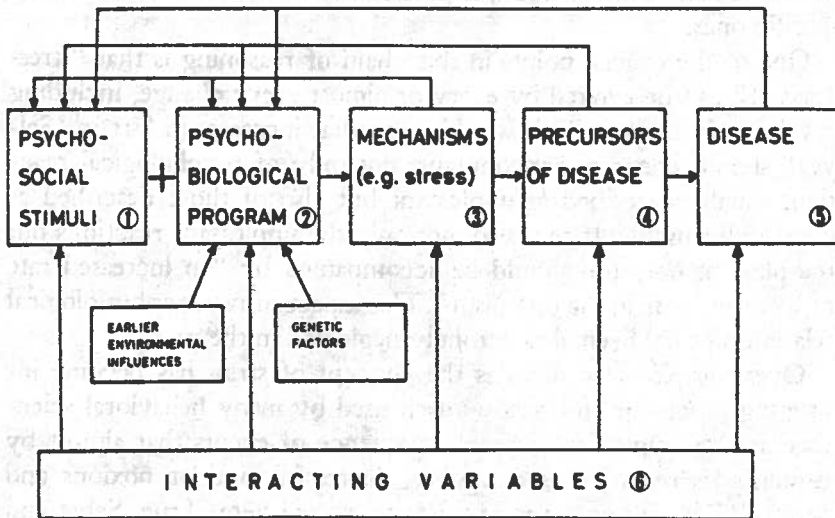
Figure II-1. A conceptual model for psychosocially mediated disease (Fig-
ure from Levi[11]).

in common with his prehistoric ancestors and with all primates, the neuroendocrine system becomes activated, preparing the organism for physical activity, e.g. fight or flight, even in situations where such reactions are clearly inadequate. The resulting increase in "stress (Selye)" may lead to an "increased rate of wear and tear" in the organism, and in predisposed individuals eventually lead to disease of one type or another.

Should this be so, one might expect (a) that a great variety of stimuli, physical as well as psychosocial, would, directly or indirectly,[ss] evoke physiological responses, some features of which (e.g. changes in sympathoadrenomedullary activity and possibly in plasma lipid level) are stereotyped and nonspecific, (b) that a positive and statistically significant relationship should exist between the degree of life change[ss] and sympathoadrenomedullary activity (as reflected in adrenaline excretion) and between life change and various types of morbidity, and (c) that hyperlipoproteinemia should predict not only death in degenerative myocardial disease but also death in general, being a mechanism, a predictor and/or precursor in a nonspecifically evoked pathogenetic process. Evidence supporting these hypotheses would point to the existence of a common, general, nonspecific factor in the pathogenic process, in addition to a number of more or less specific ones.

One of the crucial points in this chain of reasoning is that "stress (Selye)" can be evoked by every or almost every change, including psychosocial change. This would mean that increases in "stress (Selye)" should occur as concomitants not only of psychological reactions usually described as unpleasant but also of those described as clearly pleasurable. If this is so, not only the unpleasant reactions but the pleasant ones too should be accompanied by "an increased rate of wear and tear in the organism." This aspect of psychophysiological relationships has been almost totally neglected in the past.

Over the past few decades the concept of stress has become increasingly popular and is now often used by many behavioral scientists and by laymen to indicate a sequence of events that almost by definition is regarded as annoying, distressful, and/or noxious and harmful. This is not the way the term is used here. True, Selye and others usually assume that "stress (Selye)" is positively related to "the rate of wear and tear in the organism," thus being potentially

harmful at least from the viewpoint of an internist. However, one should not forget that "stress (Selye)" or certain aspects of it may very well be beneficial from, say, the *performance* viewpoint, particularly when the performance involves physical activity. As to psychological performance, an inverted-U relationship has often been demonstrated between efficiency and arousal level (*cf.* O'Hanlon[50] and Frankenhaeuser[19]). In a long series of studies, Frankenhaeuser and her group have shown that high adrenaline excretors usually perform significantly better in tasks involving perceptual conflict, choice-reaction and under-stimulation, but not in those involving over-stimulation, where the opposite is the case.

TYPE OF EVIDENCE TO BE REVIEWED

The relationships shown diagramatically in Figure II-1 have been studied in several kinds of investigation, in animals and in man.

In neurophysiological studies, different parts of the brain have been stimulated chemically or electrically and concurrent psychic and physiologic reactions have been measured to clarify pathogenic mechanisms.[1,48] In studies making use of psychological, sociological and epidemiological methods, groups of patients and matched control groups of healthy subjects have been compared for recent or premorbid exposure to various psychosocial stimuli, or with respect to "program" or interacting variables. Studies have been prospective or retroprospective. They show associations between psychosocial stimuli or interacting variables and mechanisms, between mechanisms and precursors of disease, and between psychosocial stimuli and disease. Attempts have also been made to assess the relative importance of genetic and environmental factors in the pathogenic process by comparing uniovular and biovular twins who were subjected to different environmental influences after birth. Studies have also been made of the entire pathogenic process as represented in Figure II-1, subjects or groups with certain characteristics being exposed to psychosocial stimuli assumed to be noxious, and the reactions in terms of mechanisms, precursors and disease being studied over time. Studies with precursors and *diseases* as endpoints have been made on animals, and analogies have been made with respect to corresponding processes in man. Generally, two classes of psychosocial stimuli have been applied: the specific and the nonspecific.[69]

The *specific* stimuli have little or no effect in themselves and assume

significance only because of their capacity to act as signals and symbols. The nature and degree of the psychological and physiological reactions they evoke are dependent mainly on individual past experience. Symbols that are gravely threatening to a certain individual may be meaningless to a neutral observer, and vice versa.

The other approach involves *nonspecific* stimuli, which influence the mechanisms in almost every subject whatever his past experiences, although the degree of the reaction may vary considerably from individual to individual.

In both cases, the responses are markedly modified by a great number of interacting variables. Some of these variables have been experimentally manipulated.

Some of these studies will be referred to below as evidence of a relationship between psychosocial stimuli, interacting variables, mechanisms, precursors of disease and disease. Where possible we will indicate whether this relationship is certain, probable or speculative.

PSYCHOSOCIAL STIMULI AND PHYSIOLOGICAL MECHANISMS

Some General Considerations

First we will discuss some of the psychosocial *stimuli* that have been suspected to be pathogenic, under certain circumstances and in certain individuals.

As mentioned above, every psychosocial (or physical) environmental change can evoke "stress (Selye)." A perusal of the literature leaves the reader with the impression that the relationship between psychosocial stimulation and "stress (Selye)" can be best described as a U-shaped curve, *cf.* Figure II-2. The highest stress levels are usually found at the extremes of the stimulation continuum, i.e. during the exposure to over- or under-stimulation. In general, deprivation or excess of almost any influence is found to be stress provoking in Selye's sense of the word. For instance, high stress levels may be induced during sensory deprivation and sensory overload, in response to extreme affluence as well as to extreme poverty, parental over-protection as well as parental deprivation, extreme permissiveness as well as extreme restriction of action, etc.[5, 30, 31]

In an impressive series of studies, Rahe[53] has demonstrated the pathogenic significance of the degree of life change, although his
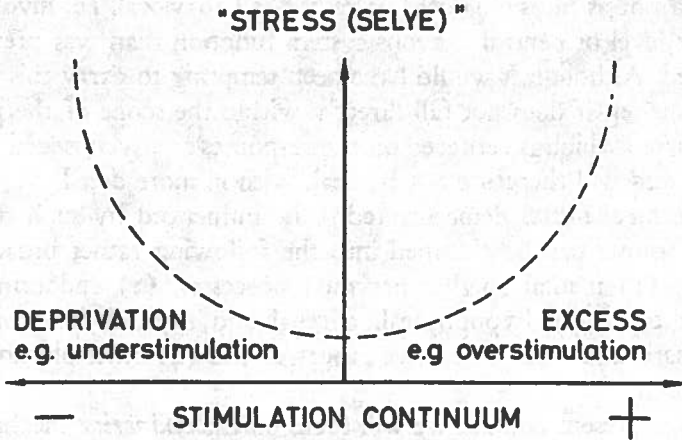
Figure II-2. Relation between physiological stress and level of stimulation. (Fig. 1:3 from Levi.[6]).

studies did not cover the mechanisms involved. Rahe's model of the relationship between life change (the sum of pleasant and unpleasant changes) and morbidity seems to be unipolar, i.e. the higher the life change, the greater the risk for subsequent morbidity. One is tempted to consider whether the model shown in Figure II-2 is applicable to Rahe's general hypothesis too. If so, life change could be just another example of stimulation, which would mean that very low as well as very high degrees of life change would be accompanied by high levels of "stress (Selye)."

Examples of experimental psychosocial stimuli will be given later in the present chapter. Suffice it to emphasize that many of the stimuli are not "purely" psychosocial and that very often the experimental or "real life" condition exposed the subject to a rather complex mixture of stimuli, which makes it extremely difficult indeed to demonstrate that a certain reaction, precursor or disease is causally related to this or that specific psychosocial stimulus.

In his penetrating discussion of the *nonspecificity* concept in stress theory, Mason[43] further emphasizes the difficulties implied in all attempts to partial out the primary effects of purely physical stimuli (e.g. cold, heat, physical trauma, physical exertion) from the secondary effects elicited by *psychological reactions* to them. At least with reference to adrenocortical function, he puts forward the alternative hypothesis that the nonspecificity and stress concepts should be re-

garded not as physiological but rather as behavioral, i.e. involving a higher level of central nervous system function than was previously realized. Although it would have been tempting to carry this discussion further, it does not fall directly within the scope of the present discourse (which is centered on the responses to psychosocial stimuli only) and will therefore not be dealt with in more detail.

The *mechanisms* demonstrated to be influenced by such psychosocial stimuli can be classified into the following rather broad categories: (1) mental (higher nervous) processes, (2) endocrine processes, especially hypophyseal, adrenal and thyroid function, (3) lymphatic and immunoreactive processes, and (4) other physiological processes.

In the present context we will focus on the *endocrine* mechanisms, particularly on the secretion of adrenaline, noradrenaline, corticosteroids and thyroxine. Although there probably are many other endocrine mechanisms, these have been considered particularly relevant and studied most.

Sympathoadrenomedullary Activity

It is well established that the sympathoadrenomedullary system is influenced by a great variety of psychosocial stimuli in animals as well as in man.[59] It has been claimed that if a sympathoadrenomedullary stimulation lasts too long or is repeated too often, the result will first be functional disturbances in various organs and organ systems.[11] It has further been hypothesized that such a dysfunction, if long-standing and/or intense, may result in permanent structural changes of pathogenic significance at least in predisposed individuals.[49, 52, 67] The theory that the sympathoadrenomedullary system reacts by an increased secretion of adrenaline in various emergency states, including those elicited by psychosocial stimuli, was put forward by Cannon and summarized by him as early as 1929. Twenty-five years passed, however, before this increased secretion was actually demonstrated.

In 1954, using Euler's new, sensitive, fluorimetric methods, Euler and Lundberg[17] first demonstrated an increased urinary catecholamine excretion in air force pilots and passengers during ordinary flight, and they attributed this to the psychosocial stimuli arising from the situation to which the subjects were exposed. In 1957 and 1958, Elmadjian, Hoagland and their collaborators at the Worchester

Foundation published data demonstrating an enhanced urinary catecholamine excretion in professional hockey players as well as in amateur boxers and psychiatric patients in situations comprising a variety and combination of psychosocial and physical stimuli.[13] Using a composite program of emotionally charged films, a stimulus that can be considered to be rather "purely" psychosocial, Euler et al.[15] demonstrated that this type of stimulus was equally effective in evoking such catecholamine reactions.

Since then, enhanced sympathoadrenomedullary activity has been demonstrated in response to a wide variety of situations comprising psychosocial stimuli[38] and a variety of laboratory situations characterized by over-stimulation, under-stimulation, anticipation and conflict.[19]

These studies clearly imply exposure to psychosocial (several of them also to physical) stimuli. However, some of these exposures have been of relatively short duration, while others clearly do not belong to the everyday experience of an ordinary population.

However, a number of the stimuli used in studies at our laboratory[20] do relate closely to habitual activity and some have been of prolonged duration. In *laboratory* studies, groups of subjects have been exposed to a variety of psychosocial stimuli including: (a) simulated industrial work (sorting of steel balls), (b) simulated office work (proofreading), (c) appearance before an audience, (d) film programs chosen to induce anxiety, aggressiveness, and other emotional reactions, (e) simulated psychomotor tasks, and (f) prolonged function under simulated ground combat conditions. In a series of *field* studies, the reactions of various occupational groups to real life stimuli have been studied, namely, the stimuli arising from the subjects' own work situation. These situations included those facing (a) telephone operators, (b) invoicing clerks and IBM operators paid a salary, (c) the same subjects paid on a piece-work basis, (d) office clerks subjected to changes in work environment (conventional offices and office landscapes, and different noise levels), (e) supermarket cashier girls (during rush hours and ordinary conditions), (f) paper mill workers working in three shifts, night and day, and (g) engine drivers working irregular shifts at various seasons.

Further data indicating an increased liberation of catecholamines in response to variety of psychosocial stimuli or in different states of

emotional arousal have been presented in detail elsewhere[38] and clearly indicated that psychosocial stimuli do, indeed, influence sympathoadrenomedullary activity.

Adrenocortical Activity

Increased adrenal cortical activity has been noted in response to many threatening life situations[38] whereas viewing Disney naturestudy films actually lowered the 17-hydroxycorticosteroids in plasma.[24]

For review in the field of psychosocial stimuli and adrenal cortical response see Hamburg,[22] Berkun et al.,[2] Rubin and Mandell[59] and Mason.[39] Briefly, it is generally agreed that adrenal cortical stimulation occurs in response to a variety of psychosocial stimuli, but that the hypophyseoadrenocortical system reacts more slowly and requires somewhat higher stimulus intensities before reaction than does the hypothalamoadrenomedullary system. A comprehensive discussion of the reactions of the hypophyseoadrenocortical system is to be found in Yates and Maran.[70]

Thyroid Activity

The evidence concerning the relationship between psychosocial stimuli and thyroid function is less conclusive. Stimulation of the anterior hypothalamus or median eminence as well as of the hippocampal formation produces a definite increase in thyroid hormone secretion, as does stimulation of the cervical sympathetic nerve and the vagal nerve.[45] According to Rees and Moll,[55] the hypothalamus is involved in the maintenance of the secretion rate of thyroid stimulating hormone (TSH) under normal conditions, possibly through the mediation of a thyrotropin-releasing factor.[46] A long-acting thyroid stimulator (LATS), probably of pathogenic significance in Grave's disease, has also been reported.[36,44,46] Recently, Persky et al.[18] reported a statistically significant relationship between LATS and Thematic Apperception Test (TAT) and Holtzman test hostility content as well as between emotional arousal and TSH.

A variety of hormones, the catecholamines probably being the most potent and physiologically important, have been reported to influence thyroid function. Thus, adrenaline injection in man has been reported to raise TSH and protein-bound iodine (PBI) levels, without, however, altering iodine uptake;[29] on the other hand, Reiss et al.[56] report an increased uptake, with a maximum three to four

hours after the injection. As with the related problem of stressor effects on thyroid function, part of the controversy is probably explained by the tendency to apply results obtained in animal experiments to considerations of thyroid physiology in man; furthermore, there is a time and a dose dependency of catecholamine-provoked thyroid reaction in that small doses probably increase and larger doses inhibit thyroid secretion, *cf.* Soderberg[63] and Ramey.[54]

As mentioned previously, it has been found that emotional reactions due to psychosocial stimuli are accompanied by a marked increase in adrenal cortical and medullary activity in humans, *cf.* Levi.[36] Most conspicuously, there is a rise in catecholamine excretion, sometimes to levels indicative of phaeochromocytoma. It is conceivable that these endogenous catecholamines affect thyroid function in much the same way as do exogenous catecholamines, and, if so, one or more links in the hypothalamic-hypophyseal-thyroidal chain are used as a target area.

Against this background, many studies have been made in which animals have been exposed to various environmental stimuli. The results are diverse and conflicting. This may be due, at least in part, to (a) differences preceding stimulus exposure, (b) specific effects of the various stimulus procedures applied, and (c) reactions specific to the species of mammals used in the experiments, in addition to the more obvious factors of (d) assay methods, (e) variations in attempts to control extraneous influences like dietary and nondietary iodine intake, and (f) criteria of thyroid function.

Exposure of sheep to insertion of a cannula into the jugular vein has been reported[18] to produce rapid but transient rises in plasma protein-bound iodine (PBI) and [131]PBI. Subsequently, after these changes had subsided, similar rises were demonstrable after a series of firework explosions, and, most consistently, after exposure to a barking dog. These rises lasted up to two hours. The same authors reported that restraint was followed by an increase in [131]PBI, but after training no such effect was observed.

As to previous studies in man, a number have attempted to relate different psychiatric clinical states[9, 23, 41, 46, 40] and fluctuations in these states to the thyroid function of the patients in question. Thus, Board et al.[8] reported PBI levels distinctly higher than in controls in thirty patients within twenty-four hours of their admission to the psychi-

atric section of a general hospital. Similarly, Hetzel et al.[27] reported increases in serum PBI in euthyroid patients subjected to stressful real-life experiences. Related results have been reported by Klein-sorge et al.[32]

Wolff[68] described fluctuations in plasma protein-bound iodine in association with exposure to stressful life experiences. Increases of as much as 100 percent were recorded in some subjects. Some changes took place within an hour of the beginning of the stimulus exposure, a psychiatric interview. In a similar investigation, Tingley et al.[66] examined the protein-bound iodine on control days as well as on stress days (exams for the medical student subjects) and found significant increases during the latter conditions. Similarly, three out of four medical students, exposed to an important examination, reacted with a significant elevation of thyroidal [132]I uptake.[7] More recently, Persky et al.[51] and Dewhurst et al.[10] have reported a statistically significant relationship between emotional reactions of various kinds and TSH levels. Exposing a total of sixty-three army officers and corporals to a seventy-five-hour vigil including seventy-two hours of intellectual performance and/or performance in an electronic shooting range under controlled environmental conditions. Johansson et al.[28] demonstrated a highly significant increase in protein-bound iodine, in individual cases to levels clearly above what are usually considered normal limits. This study is reported in detail by Levi.[38] Briefly, then, it may be concluded that a variety of psychosocial stimuli may elicit significant increases in protein-bound iodine as well as in other indices of thyroxine release in animals as well as in man.

Psychosocial Stimuli: Influence on Human Physiology

Thus, there is good evidence for a variety of effects of psycho-social stimuli on neuroendocrine function. The neuroendocrine reactions thus elicited can, theoretically, in turn influence all or nearly all existing physiological variables.

The thyroid hormones have been shown to increase the turnover of carbohydrates, lipids, calcium and magnesium, the heart rate and contractility, and total peripheral resistance, the secretion of hydro-cortisone and growth hormone, and the sensitivity of some tissues to the catecholamines. The catecholamines are powerful vasoactive agents with pronounced effects on carbohydrate and lipid metabo-

lism. The adrenal cortical hormones regulate, among other things, the carbohydrate metabolism and the metabolism of minerals and water. Consequently, a very large number of physiological processes are influenced, directly or indirectly.

In summary, we know that psychosocial stimuli cause physiological changes, which in turn *could* lead to precursors and disease.

INTERACTION VARIABLES, PRECURSORS AND DISEASE

Interacting variables may be predisposing or protective. Either may be extrinsic (environmental) or intrinsic. Many predisposing interacting variables that appear to be physical in nature may have a psychical element, e.g. heat, noise, overcrowding, malnutrition (cf. Mason[12]). Many of the protective interacting variables are of a psychosocial origin, e.g. habituation, adaptation, coping and substitution. Partly depending upon the presence, or absence, of such interacting variables, psychosocial stimuli may or may not influence physiological mechanisms, precursors or even disease itself.

Some of the psychosocially evoked changes in physiological function do in turn evoke proprioceptive signals to the cerebral cortex. In some individuals, and under certain circumstances, even perfectly "normal" signals of this type may be interpreted by the individual as symptoms of disease (as in the case of hypochondriasis). If the psychosocial stimulation exemplified above is pronounced, prolonged or often repeated, and/or if the organism is predisposed to react because of the presence of predisposing or absence of protective interacting variables, the results may be hyper-, hypo- or dysfunction in one or more organs and organ systems. Examples of such reactions are tachycardia and palpitations, vasovagal syncope, pain of vasomotor or muscular origin, hyperventilation, increased or decreased gastrointestinal peristalsis, etc. These reactions may, but need not, be accompanied by unpleasant emotional reactions such as anxiety, depression, apprehension, etc.

It is often postulated that the development of psychosocially induced diseases is preceded by a "precursor" state characterized by malfunction of mental and physiological systems without apparent disability.

However, as mentioned in connection with the definitions, it is sometimes impossible to demarcate the mechanisms from the precursors or from disease itself. This is particularly so when, in clinical

practice, the mechanism and, more often, the precursor, is given the disease label, e.g. as in the case of *gastrointestinal distress*. Thus, there is no sharp borderline between "normal" reactions on the one hand and hypochondriacal reactions and psychological and/or physiological dysfunction characterized as precursors or diseases on the other. Besides, the definition of the level where normality ends and disease begins is closely interrelated with the social psychology of labeling.[18] Evidence concerning the reactions described above has been reviewed elsewhere.[4, 8, 11, 21, 34, 37, 57, 61, 64, 65, 67]

Further, psychosocial stimuli may also influence health by impeding recovery and aggravating disability, whatever the etiology of the primary disease. Such a psychosocially induced response may be rooted, for example, in an intense anxiety over the disease or the situation, and possibly complicated by secondary gains such as utilization of the disease as a means of avoiding responsibility, justifying one's incapacity and providing a release from social pressure.

The precursors and diseases mentioned above are all clearly influenced by psychosocial stimuli. They are all characterized by disturbed function of one type or another, but presumably not by more or less chronic functional or even structural changes. The role of pyschosocial stimuli in the etiology and pathogenesis of "psychosomatic diseases" where such changes have taken place (as in the case of peptic ulcer, bronchial asthma, essential hypertension, thryotoxicosis, and degenerative heart disease) is less clear, partly because so little is known about the etiology and pathogenesis of these disorders.

According to some of the hypotheses mentioned above, the human organism's pattern of response to a variety of environmental stimuli, including the psychosocial ones, constitutes a phylogenetically old adaptational process ("stress" in Selye's sense), preparing the organism for physical activity, usually for fight or flight. However purposeful these activities may have been in the dawn of the history of mankind, they have ceased to be very adequate in the adaptation of modern man to the endless number of socioeconomic changes, social and psychological conflicts, and threats involved in living in a highly industrialized modern, urban society. Furthermore for social reasons, man has to repress many of his emotional outlets and motor activities. This creates a situation in which there might very well be a disintegration between the expression of emotion, the neuroendocrine con-

comitants of emotion and the psychomotor activities likely to accompany such emotion. For example, in a marital or occupational setting, modern man may feel anxiety or aggression and exhibit the neuroendocrine concomitants of the emotional reaction without showing it in his facial expression or verbal or gross motor behavior. On the other hand, situations do occur when man is compelled to exhibit emotional expressions and to perform physically or verbally in a way grossly incongruous with his actual neuroendocrine and emotional state. If this "stress" pattern of response to psychosocial stimuli and/or this psychophysiological discrepancy lasts long enough, it has been suspected to be of pathogenic significance. Indeed, processes of this kind have been claimed to constitute a major factor in the etiology of several diseases in the field of internal medicine. An early notice of this psychosomatic relationship is to be found in Ecclesiastes 30:24 (about 200 B.C.), indicating that "envy and wrath shorten the life."

The evidence for and against this and related hypotheses comes primarily from animal experiments, epidemiological studies, and physiological measurements and observations in clinical practice. A detailed presentation and discussion of such data fall outside the scope of this chapter. In this context, it may suffice to recall the proposed relation between psychosocial stimuli and catecholamines, plasma lipids, corticosteroids, thyroid function and electrolytes, and to mention the relationship between catecholamines, hyperlipidemia and atherosclerosis, and the combined action of catecholamines, corticosteroids, thyroid hormones and potassium deficiency in degenerative heart disease.

PSYCHOSOMATIC RESEARCH
Some General Considerations

"Scientific study of emotion and of the bodily changes that accompany diverse emotional experience marks a new era in medicine. We know now that many physiological processes which are of profound significance for health . . . can be controlled by way of emotions. In this knowledge we have the key to many problems of prevention and treatment of illness." This was written some thirty-five years ago, by Flanders Dunbar, in the introduction of her first large survey of experimental and clinical studies in the field of "emotions and bodily changes." However, in spite of the innumerable studies

published since, part of which have been reviewed above, this "key to many problems of prevention and treatment" has been elusive, and we are still confronted with a confusing variety of controversial *data* on psychosomatic relationships, not to mention the interpretations of and the hypotheses built on these data.[42]

A perusal of the literature in this field, however, leaves the reader with a feeling that part of this controversy might have been avoided (a) by more attention being paid to methodological problems and (b) by subjecting the various links in the hypothetical chain of events mentioned above (Fig. II-1) to a more systematic and comprehensive study. Here, we review previous knowledge and suggest some new ways of examining Mason's key question,[43] "What normal body mechanisms are involved in psychosomatic illnesses and how and why do they go wrong?"

Psychosomatic research is primarily concerned with physiological and psychological reactions induced by environmental stimuli that are usually referred to as "psychosocial." In most of the psychosomatically oriented medical literature, various disorders have been related to a number of such stimuli to which the patients usually are said to have been exposed prior to and/or in conjunction with the onset of the particular disease.[35].

The constellations of these stimuli inherent in everyday life—at work, in the family, even in the clinical situation—are, however, usually very complex and the interaction with physical stimuli of many types complicates the picture still more. It is, therefore, very difficult clinically or even epidemiologically to distinguish between the various links in the hypothetical chain of events and to map out the relative importance, if any, of one or another of the many psychosocial influences.[47]

As a complement to clinical and epidemiological studies, researchers in various disciplines and parts of the world have increasingly made use of psychophysiological and psychoendocrine experiments by exposing an individual or a group to various *stimuli*, single or combined, intense or moderate, of long or short duration, etc. Or a stimulus has been applied to various *individuals* or *groups*—patients and healthy controls, females and males, young and old, extroverts and introverts, people who do or do not make use of various coping mechanisms, etc. In either case, we may want to study psychological

and/or physiological functions at various levels of complexity, using different methods of measurement and different "languages" in describing the reactions and their underlying mechanisms. Theoretically, we would like to study the entire sequence of events in all relevant groups when exposed to all relevant stimuli, the measurements comprising all relevant variables. This, of course, is not possible. Therefore, in medical research, we are likely to concentrate on stimuli and mechanisms suspected by some as potentially of pathogenic significance, or on individuals or groups likely to be more (or less) at risk than the general population.

The Stimuli

The use of different kinds of functional and provocation tests has long been practiced in physiology and clinical medicine, the patient being exposed to such stimuli as physical work, ACTH, insulin, cold and allergens, in order to test the quality and quantity of his response. The psychophysiological experiment makes use of psychosocial stimuli in a corresponding way, by exposing subjects to (a) threats to self-esteem or physical integrity, (b) various types of high or low sensory input, (c) open-ended situations or (d) environmental change in general, of varying magnitude, frequency and/or velocity.

As already mentioned, these stimuli may be specific, i.e. have a special meaning for the subject, or *nonspecific*, that is to say active to some extent on all individuals irrespective of the subject's genetically and environmentally determined psychobiological "programming."[10]

In a review of psychophysiological stress studies, Harris et al.[15] classified experiments of this type according to the kind and duration of stimulus employed. According to these authors, short-term stimuli may be exemplified by and categorized into: (1) failure stressors (e.g. subjects told about previous failures but given one more chance to solve insoluble problems), (2) workload, pacing and distraction stressors (e.g. subjects have to perform a task, sometimes at above-normal speed, sometimes being distracted by meaningful or meaningless noises, flashing lights, electric shocks, etc.) and (3) fear-inducing stressors (real or simulated threats of criticism, of being fired, of physical danger, or unpredictability implied in the stimulus situation, etc.).

Long-term stimuli are similarly subdivided into four categories: (1) combat stressors (subjects are exposed to attack situations or a defensive stand over long periods of time), (2) stressors of hazardous duty (e.g. of submarine and aircraft personnel, or soldiers near the front line area but not in actual battle), (3) stressors of confinement and isolation (e.g. submarine or astronaut duty, prison confinement, low sensory input) and (4) prolonged performance stressors (vigilance tests, monotonous work, etc., resulting in fatigue).

Most of the short-term studies have been performed in psychological or physiological laboratories, whereas the long-term stressors are often given in a real-life setting. Many of the laboratory studies have been well designed scientifically but may lack realism and meaning to the subjects tested. The real-life situations, on the other hand, usually have been realistic enough but in many cases badly controlled, and so their results are indecisive.

Interacting Variables

It is common knowledge that different individuals do not react identically to any given stimulus or set of stimuli. Neither does an individual react identically on various occasions even if we try to keep the stimulus conditions reasonably constant. The reasons for this inter- and intra-individual variability are manifold—processes like habituation, adaptation, learning and coping, constitutional factors, genetic as well as acquired group interaction, interaction effects with other stimuli, just to mention a few. Factors like these must be taken into account when choosing our subjects and the circumstances for their study.

Reactions

On the reaction side, a study of "emotions and bodily changes" usually implies simultaneous determination of these two sets of variables and an analysis of the relation between them, if any. Trying this, we face a series of problems. Needless to say, the actual, subjective experiences of our subjects are not accessible to direct measurement, neither are the basic neuroendocrine processes which are closely linked to these experiences. We have to be content with indirect studies of these phenomena, e.g. the subject's verbal report of his experiences, or measurements of hormone levels in body fluids.

A very large number of such psychological and physiological variables have been described and measured in man's response to various

psychosocial stimuli. Psychological responses have been measured by direct observation, by interviews, questionnaires and projective techniques. A great number of physiological measurements have dealt with various aspects of cardiovascular, respiratory, gastrointestinal and renal function, each study usually focusing on a few variables, and without paying much attention to the underlying physiological mechanisms, treating them as a "physiological black box."[42]

What To Measure and Why

Another set of studies—including those by the present author—have dealt not so much with specific organ functions but with the more basic, integrative aspects of physiological response, i.e. the neuroendocrine reactions. During the last two decades, chromatographic, isotope, immunoassay, microspectrophotometric and fluorimetric methods of measurement have become available that allow a relatively detailed study of functions related to what is commonly called the hypophyseoadrenocortical and hypothalamicoadrenomedullary axes. In man, these functions have usually been studied by determining various hormones (and compounds, influenced by these hormones) in blood, urine, liquor and in various tissues.

In some of these studies, the psychological responses were assessed simultaneously, with respect to self-ratings by the subjects, and to performance when work of one type or another was involved.

The primary target for the studies conducted at our laboratory has been the human organism's sympathoadrenomedullary activity measured as urinary excretion of adrenaline and noradrenaline, analyzed fluorimetrically.[16] This set of variables was chosen for several reasons. First the responses of the sympathoadrenomedullary system have been studied less than those of the adrenocortical system, partly because satisfactory methods for assay of hormones belonging to the last-named system have been available for a longer period of time. Second, it is known that the catecholamines may play important roles in the physiology of the human organism, in health as well as in disease. Third, earlier studies conducted by the present author and by others gave reason to suspect a rather close relationship between sympathoadrenomedullary and psychological function.

Some of the studies comprised measurements of other physiological variables as well (e.g. plasma lipids, erythrocyte sedimentation rate, serum iron, protein-bound iodine, urine flow and specific gravity,

urinary creatinine, ECG pattern), to provide data relevant to specific objectives of the study."

GENERAL OBJECTIVES OF OUR STUDIES

Investigations from our laboratory all had the following general objectives in mind.

Firstly, to ascertain whether, and, if so, to what extent exposure to some psychosocial stimuli encountered by modern man (e.g. piecework) actually elicits significant changes in sympathoadrenomedullary and other physiological functions as reflected in changes in a number of blood and urine constituents. Should this be so, it may turn out to be necessary to take the psychosocial situation of the patient into account when clinically interpreting laboratory data on these constituents.

Secondly, to find out whether any physiological reactions provoked in this way have a reasonably high and steady correlation with the subjective state experienced and, one may hope, reported by the subject. The objective would be to see if the physiological reactions could be used as a predictor or index of subjective reactions in cases where these are not readily accessible to direct measurement with psychological methods,[13,14] as an index which cannot be masked by verbal or overt behavior.[42]

Thirdly, to study possible interindividual differences in the "programming" of the organism as reflected in differences in different groups' (males and females) reactions to identical stimuli.

Fourthly, to see if physiological reactions to psychosocial stimuli experienced under relatively long-term conditions were similar to those produced in acute laboratory experiments.

Fifthly, to identify mechanisms by which psychosocial stimuli are likely to lead to disease.

Much of the discussion to be presented in the following chapters is based on the "stress (Selye)" concept. As repeatedly emphasized by Selye, this concept should be regarded as a working hypothesis, to be evaluated and re-evaluated with refined methods. The use of this concept does not necessarily imply an unconditional acceptance of an *absolute* "nonspecificity." Clearly, there is a progressively greater burden of proof involved as we move through the sequence of hypotheses that a particular bodily response is evoked (a) in a relatively great diversity of situations, to (b) by a relatively great di-

versity of stimuli, to (c) by "*every* stimulus." At the present stage, all of these hypotheses seem to deserve evaluation.

THE "STRESS (SELYE)" CONCEPT

As demonstrated in a number of investigations in our laboratory, psychosocial stimuli do clearly influence urinary catecholamine excretion, either enhancing or lowering it, depending on the stimuli and on the psychophysiological starting position of the organism. Enhancement occurs not only in response to stimuli which most subjects rate as predominantly "unpleasant" but also when the self-ratings indicate predominantly "pleasant" emotional reactions in most of the subjects. We interpret these data as supporting the hypothesis concerning "stress (Selye)" as the nonspecificity (or stereotypy) of physiological reaction to a variety of stimuli, taking into account not only "unpleasant" reactions but "pleasant" ones as well. Probably it is the intensity, and not the quality of these reactions which is the main correlate of "stress (Selye)." Our results further support the assumption that sympathoadrenomedullary activity constitutes part of "stress (Selye)."

Of course, this is not meant to imply that no specific relationship exists between psychosocial stimuli and physiological response, or between subjective response and physiological concomitants. On the other hand, our findings do not support hypotheses proposed by other authors concerning a specific relationship between, for example, anxiety and adrenaline excretion or between aggression and noradrenaline excretion. This interpretation is in agreement with findings reported by Frankenhaeuser and her group.[19]

True, the "stress (Selye)" nonspecificity in physiological response discussed so far relates exclusively to *psychosocial* stimuli. On the other hand, it is well-known that a considerable number of *physical* environmental stimuli do evoke a similar response, *inter alia* involving sympathoadrenomedullary activity.

As indicated previously, there can be several *degrees* of nonspecificity in bodily response, the same reactions occurring in response to (a) relatively great diversity of *situations*, (b) a relatively great diversity of *stimuli* (physical and/or psychosocial) and (c) *every* stimulus. Our results do not allow any definite statement as to which of these alternatives is most valid, but they do contribute to illustrate

the nonspecificity postulated by Selye and emphasize the need for further research in this field.

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CHAPTER 5

STRESS, DISTRESS AND PSYCHOSOCIAL STIMULI

LENNART LEVI

THERE IS NO QUESTION but what environmental *physical stimuli* cause disease. This has been well established for a large number or factors and diseases. As the exposure, avoidance or manipulation of physical factors increases or decreases, the chance of becoming ill or reversing ill health occurs.

The role of *psychosocial stimuli* is not so clear. This chapter will present a perspective on the relationship between such stimuli and various factors associated with physical disease. First, it will focus on theoretical concepts which relate to the development of psychosomatic disorders. Next, it will illustrate various aspects of these matters with data from recent studies. Finally, it will present some viewpoints on the prevention of psychosomatic disorder.

PSYCHOSOCIAL STIMULI, STRESS AND DISEASE

Stress will be a major consideration in this discussion. The term "stress" is used as Selye has used it. That is, the *non-specific response of the body to any demand made upon it* (Selye, 1971). The intensity and duration of this stereotyped, phylogenetically old adaptation pattern which prepares the organism for fight or flight is assumed to be closely related to the rate of wear and tear in the organism. Consequently it is probably also related to the morbidity and mortality. Stress as used here is not only related to any *specific* disease but is probably associated with a variety of diseases. In other words, if environmental changes occur frequently and/or are of great magnitude and/or if the organism is particularly vulnerable, stress reactions usually increase in intensity and duration. This is shown in Figure

5-1 which demonstrates the hypothetical relationship between various levels of environmental stimulation and the resultant amount of "stress Selye."

"STRESS (SELYE)"

DEPRIVATION
e.g. understimulation

EXCESS
e.g. overstimulation

STIMULATION CONTINUUM
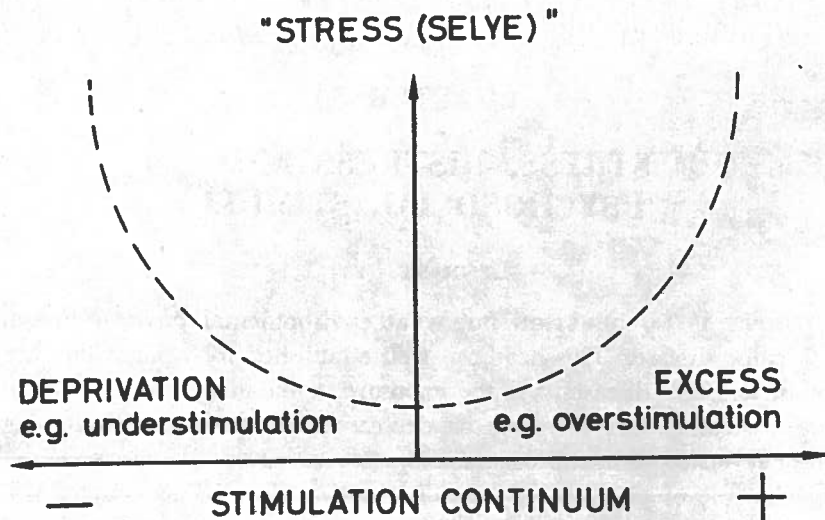
Figure 5-1. Theoretical model of the relation between physiological stress (as defined by Selye) and various levels of stimulation. According to this hypothesis, deprivation of stimuli as well as excess is accompanied by an increase in "stress (Selye)", (Levi, 1972).

Hypochondriasis, Functional Disturbance, and Structural Damage

Clinically, overt symptoms may appear even with relatively low stress levels. This occurs, for instance, if a patient pays untoward attention to sensations originating from such reactions. Thus, in some individuals and under certain circumstances, even "normal" sensations of this type may be interpreted as symptoms or disease (as in the case of hypochondriasis).

If psychosocial stimulation is pronounced, prolonged or often repeated, and/or if the organism is predisposed to react because of the presence or absence of certain interacting variables, the result may be a hyper-, hypo-, or dysfunction in one or more organs, not only in those subjects who are particularly aware of and sensitive

to their proprioceptive signals but in perfectly "normal" subjects as well. Examples of such reactions are tachycardia, syncope, pain of vasomotor or muscular origin, hyperventilation, and increased or decreased gastrointestinal peristalsis.

Almost by definition, these symptoms are detrimental to the normal *function* of the organism, as in the case of an organ neurosis. If such reactions are particularly prolonged, there is suggestive evidence that they may eventually lead to *structural* damage as well.

Given these considerations let us now examine some of the principal hypotheses in the study of psychosocially mediated disease. (See Fig. 5-2). The main hypothesis is that psychosocial stimuli can cause disease. The etiology may be specific—that is a *specific* disease may be caused by a particular stimulus. The cause can also be *non-specific*. That is, disease will occur in response to a wide variety of stimuli and/or in a wide variety of subjects.
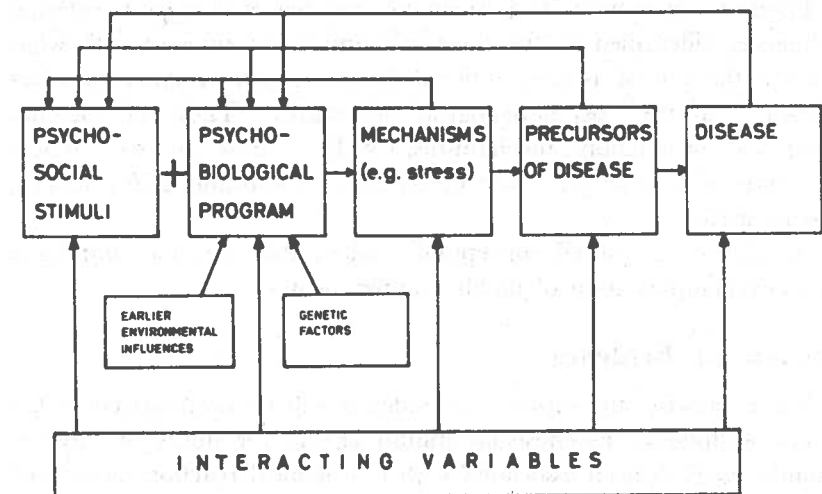
Figure 5-2. A theoretical model of psychosocially mediated disease. The combined effect of psychosocial stimuli (1) and man's psychobiological program (2) determines the psychological and physiological reactions (mechanisms) (3), e.g. "stress (Selye)" of each individual. These may, under certain circumstances, lead to precursors of disease (4) and to disease itself (5). This sequence of events can be promoted or counteracted by interacting variables (6). The sequence is not a one-way process but constitutes part of a cybernetic system with continuous feed-back (Kagan and Levi, 1971).

Hypotheses on Psychosocially Mediated Disease

In the present context I will focus on the *non-specific* etiology and will suggest hypotheses concerning disease that are psychosocially mediated:

1. Most life changes evoke a stereotyped, phylogenetically old, adaptational response pattern which prepares the organism for physical activity, e.g. for fight or flight.

2. "Stress (Selye)" is characterized by increased activity in the hypothalamo-sympathoadrenomedullary, hypophyseo-adreno-cortical, and possibly the thyroidal system.

3. The reactions, at least if prolonged, intense or often repeated, are accompanied by an increased rate of wear and tear in the organism.

4. Such generally increased rate of wear and tear leads, in the long run, to increased morbidity and mortality.

Figure 5-2 demonstrates a schematic overview that suggests external influences (identified as "psychosocial stimuli") combined with what may be thought of as constitutional factors, e.g. personality variables (labeled as the "psychobiological program"). They are together productive of reactions, mechanisms, e.g. like "stress (Selye)." These in turn may provoke precursors of disease and, continuing in evidence, disease itself.

As in the case of all conceptual models, this one, too, implies a gross oversimplification of highly complex issues.

Review of Evidence

To be concise, the supporting evidence will be summarized in the following figures. Psychosocial stimuli lasting for hours or days or months have all been associated with biochemical reactions associated with "stress (Selye)."

BIOCHEMICAL REACTIONS IN RESPONSE TO PSYCHOSOCIAL STIMULI. Figures 5-3 and 5-4 A and B demonstrate that such stimuli lasting for some hours increase adrenaline and nonadrenaline excretion and also the levels of plasma free fatty acids and triglycerides.

Psychosocial stimuli lasting several days also increase "stress (Selye)." This is reflected in the increase in adrenaline excretion noted in Figure 5-5 and in the plasma free fatty acids and cholesterol
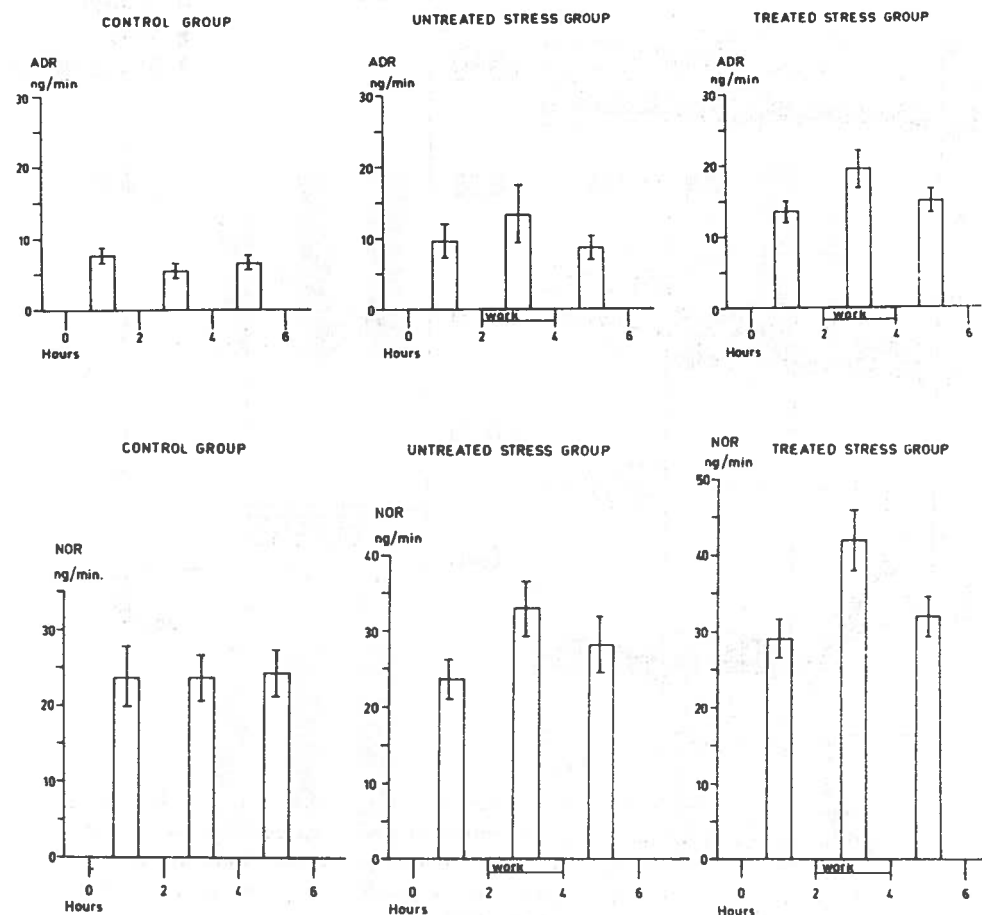
Figure 5-3. Mean ± standard error of the mean for epinephrine (top) and norepinephrine (bottom) excretion, under conditions designed to induce distress under the second of the three 2-hour periods in the untreated (center) and nicotinic acid treated (right) stressor-exposed groups but not in the control group (left), (Carlson, *et al.*, 1972).
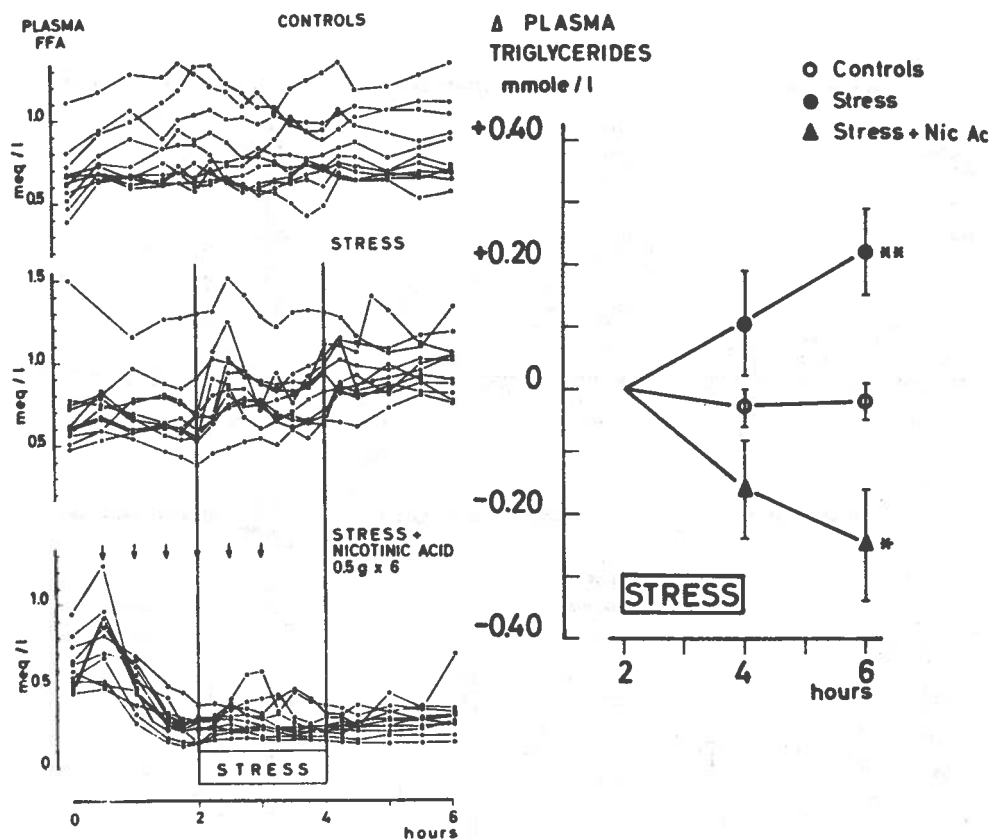
Figure 5-4. A: Individual values for arterial plasma levels of free fatty acids in the control group (top), the untreated stressor-exposed group (center), and the treated stressor-exposed group (bottom). Arrows indicate nicotinic acid administration (0.5 g 6 times, i.e. every thirty minutes in the treated stressor-exposed group (Carlson, *et al.,* 1972).

B: Mean ± standard error of the mean for the changes in plasma triglycerides during and after the second 2-hour period, which was designed to induce distress in the untreated and treated stressor-exposed group but not in the control group. * and ** indicate that p < 0.05 and 0.01, respectively (Carlson, *et al.,* 1972).
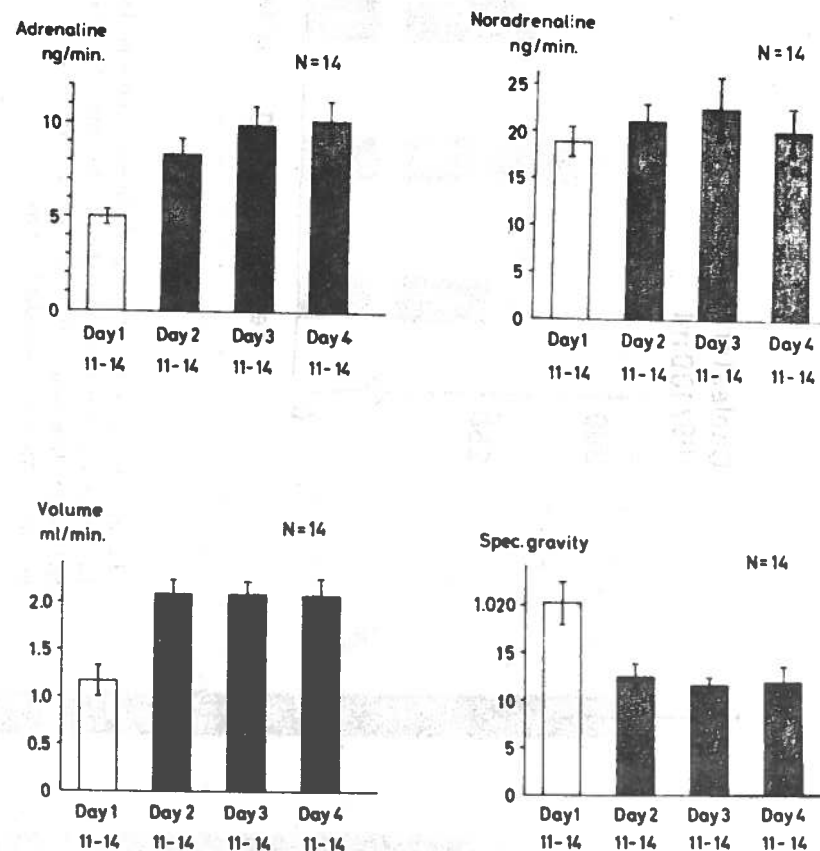
Figure 5-5. Urinary adrenaline and noradrenaline excretion, urine flow, and specific gravity during control conditions (empty bars) and corresponding periods of days 2, 3 and 4, at eleven to fourteen hours. Means ± S.E.M. (Levi, 1972).
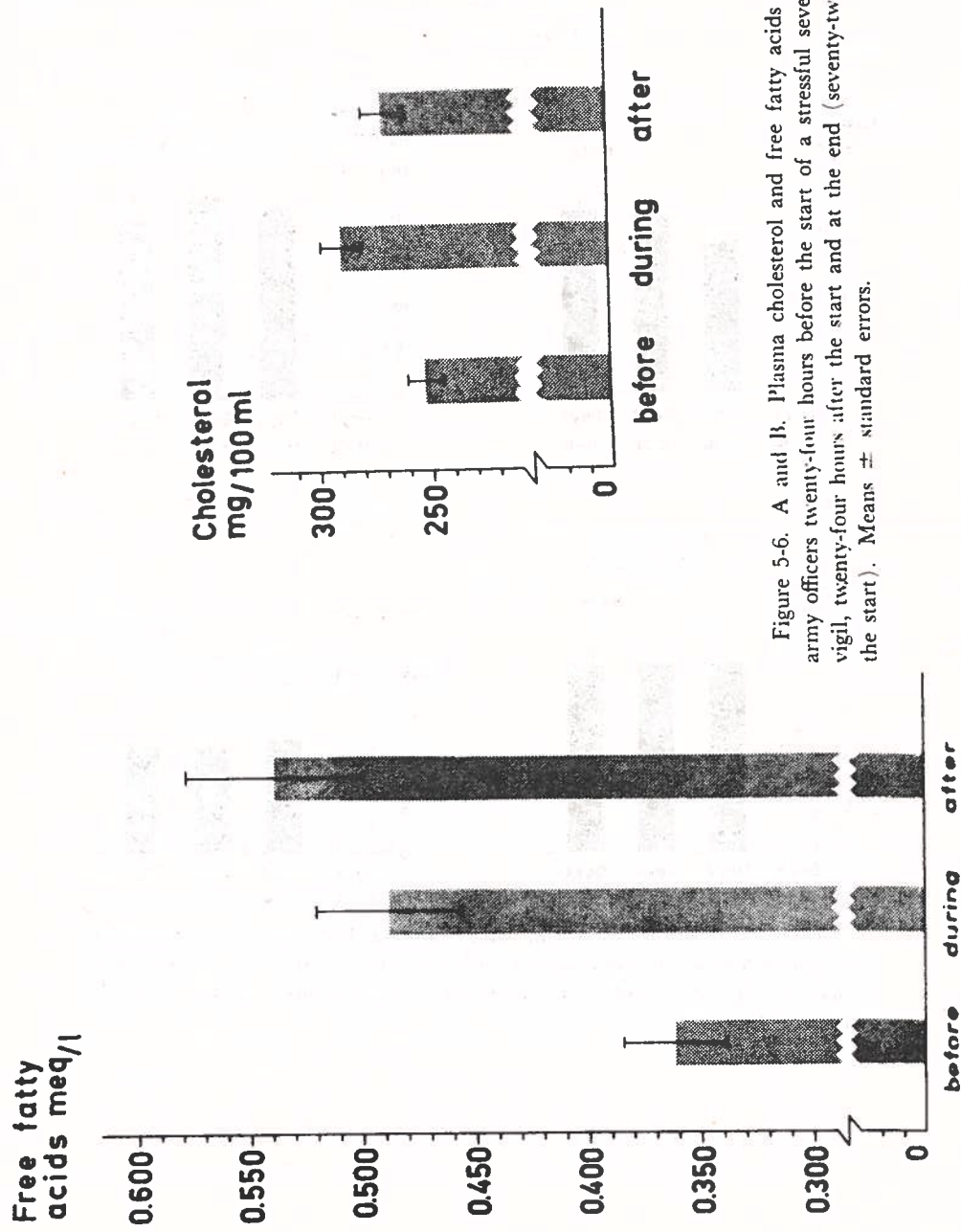
Figure 5-6. A and B. Plasma cholesterol and free fatty acids in thirty-two army officers twenty-four hours before the start of a stressful seventy-two hour vigil, twenty-four hours after the start and at the end (seventy-two hours after the start). Means ± standard errors.

Cholesterol mg/100ml

Free fatty acids meq/l

PROTEINBOUND IODINE gamma %
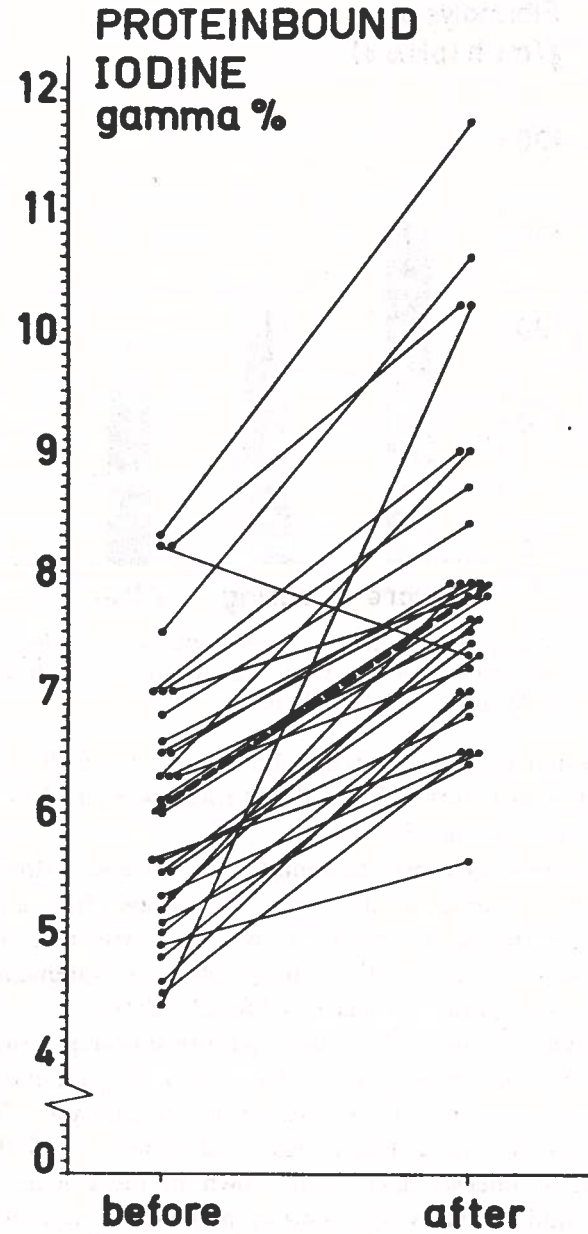
before   after

Figure 5-7. Protein-bound iodine before and after a seventy-two-hour vigil (Levi, 1972).

Fibrinolysis
γ/ml·h (pH 6.3)
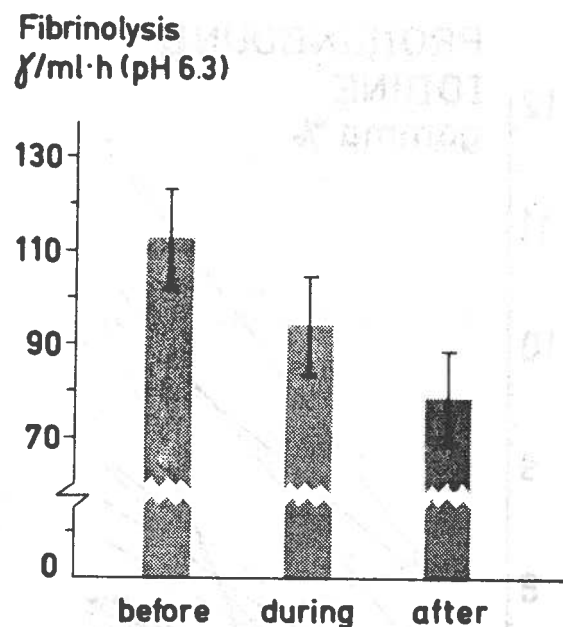
Figure 5.8. Fibrinolysis in thirty-two army officers twenty-four hours before the start of a stressful seventy-two-hour vigil, twenty-four hours after the start and at the end. Means ± standard errors.

which are shown to be elevated in Figure 5-6 A and B. The protein-bound iodine in Figure 5-7 and the fibrinolysis levels demonstrated in Figure 5-8 support this hypothesis.

Longer-acting psychosocial stimuli also increase "stress (Selye)." The evidence in support of this hypothesis is drawn from a longitudinal study demonstrating a significant, positive correlation between the reported weekly sum of "life change units" and adrenaline excretion during the days prior to interviews (Rahe, 1969).

The studies all support the hypothesized relationship between psychosocial stimuli (Figure 5-2) and potentially pathogenic mechanisms.

PSYCHOSOCIAL STIMULI AS RELATED TO DISEASE. Various life changes may be regarded as psychosocial stimuli. And these, if frequent and/or intense, have been shown to precede an increase in morbidity and mortality in a *variety* of illnesses, psychiatric as well as somatic. Holmes, Rahe and others have demonstrated that the greater the degree of change in a subject's life during a certain period of time, the higher is his risk of developing subsequent decrease in

health status (Holmes and Rahe, 1967). It may be noted that the life changes under consideration also include those usually considered pleasant such as an engagement, a marriage, and the gaining of a new family member.

A number of studies supporting this relationship between individual cumulative life changes with subsequent nonspecific health changes have been published. Among the more recent are those of Theorell (1970), and Rahe (1972) and Theorell, Lind *et al.* (1971).

There is evidence of a relationship between psychosocial stimuli and some specific diseases including thyrotoxicosis, some cardiac disorders, essential hypertension, and peptic ulcer. (For a review, see Kagan and Levi, 1971.) This evidence tends to support the relationship hypothesized in Figure 5-2.

RELATIONSHIP BETWEEN MECHANISMS AND DISEASE. Increased levels of triglycerides and cholesterol predict increased risk not only for subsequent ischemic heart disease (Keys, 1970) but also for a variety of other diseases as found by Tibblin in a large scale prospective study on males born in 1913 and followed annually since 1963. (See Figs. 5-9 and 5-10.) These findings support the relationship hypothesized in Figure 5-2 between the boxes labeled "mechanisms" and "precursors of disease" and that called "disease."

Furthermore, various diseases have been induced experimentally in animals, including primates, by exposing them to psychosocial stressors. In this way, several authors induced degenerative heart disease and hypertension (Lapin and Cherkovich, 1971). Further supporting the hypothesis of psychological stimuli as possible etiological agents in a variety of diseases.

POTENTIALLY NOXIOUS PSYCHOSOCIAL ENVIRONMENTAL CONDITIONS. From this we may conclude that environmental conditions may provoke stereotyped reactions, involving changes in bodily functioning which may be rather pronounced. These reactions include increases in catecholamine excretion and in plasma levels of free fatty acids, triglycerides, cholesterol and protein-bound iodine. They are also associated with a decrease in serum iron and fibrinolysis. The increased catecholamine output, occurring in response to almost any type of environmental change is correlated positively with the intensity of self-reported distress.

It has further been shown that subjects exposed to frequent and
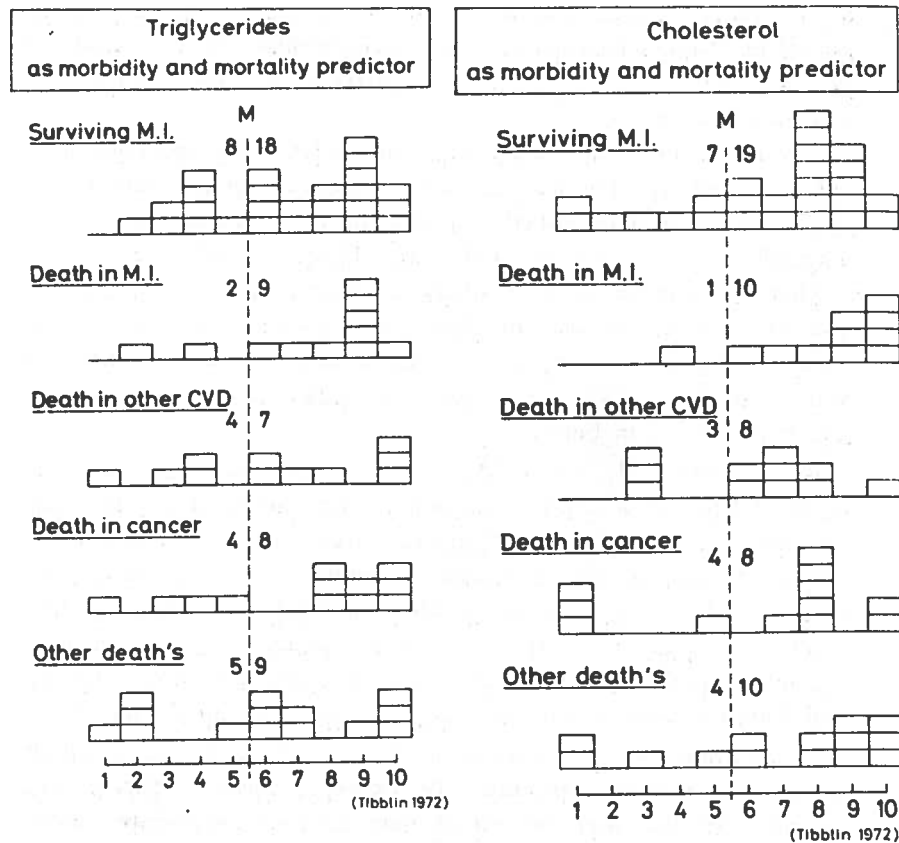
Figures 5-9 and 5-10. Plasma triglycerides and cholesterol as predictors of morbidity and mortality in myocardial infarction (M.I.), and of mortality in other diseases. Distribution in deciles (1-10) of plasma levels in relation to deaths. Vertical line indicates median. Each box indicates one death or case of illness. Figures indicate distribution of below-median (left) and above-median (right) triglyceride and cholesterol levels (Tibblin, personal communication). Above-median levels seem to predict subsequent morbidity and mortality (Levi, 1972).

dramatic environmental changes run a higher risk of developing myocardial infarction within the next six months (Theorell, 1970). Similar relationships have been demonstrated for a variety of somatic and psychiatric diseases (Rahe, 1972).

Finally, it has been found that high triglyceride and cholesterol

levels in a random population are positively related to a subsequent increase in mortality in a variety of disorders.

Taken together, the studies demonstrate the probable importance of non-specific psychosocial environmental stimuli and non-specific physiological mechanisms in the production of a variety of diseases. We further conclude that the causation of disease by such stimuli is not proven, but that there is a rather high level of suspicion. Nor are we saying that specific factors are unimportant. Both deserve and need further study, focusing on a number of psychosocial environmental factors.

MONITORING AND PREVENTION
PRACTICAL IMPLICATIONS

Before one can discuss prevention in scientific terms it is necessary to have more information. This means research, and research means both planning and measuring.

But health administrators will continue to feel that action should be taken based on the existing levels of suspicion. Whether such action is in the area of marriage counseling, crisis intervention, developing more satisfying jobs, or of programs for the aging, it is mandatory to regard the actions as only a trial. Concurrently, means must be established of evaluating the program for efficiency, safety and cost. This has both a scientific and a social purpose; the former to establish knowledge; the latter to protect individuals from danger. It also serves to avoid a sense of false security, to prevent delay in applying useful procedures, and to provide rational support for innovative measures based on known cause and effect.

Since our knowledge of psychosocial hazards and disease is relatively incomplete, much of what we say about *monitoring* for and *preventing* disease is speculative. Changes likely to expose large numbers of people to new social relationships or generally requiring them to make major adaptations may result in subsequent health hazards (Kagan and Levi, 1971). Awareness of this possibility should be in the minds of the leadership of any organization contemplating such change whether in a work organization or at the community level. If change is likely to be accompanied by removal from old forms of social support and either lack of, or failure to use, new forms, there might be a need for preventive action.

Awareness of possible hazards in any group—large or small—
may arise from the examination of morbidity records. Such data
are not likely to be conclusive in any way, but high and/or rapidly
increasing rates for suicide, neuroses, and psychosomatic disorders
may provide a community with suggestions for more detailed inquiry.
In the same way increases in sickness and accident benefits, the use
of health insurance, and accident rates may suggest to the leadership
of a work organization the need for investigation and the establish-
ment of techniques of prevention. Such prevention could focus on
rather general phenomena in large groups of subjects; that is, the
principal focus could be on deprivation or excess of a large number
of stimuli. Concerns could be with such matters as over- or under-
stimulation, lack of parental care or overprotection, poverty or
affluence, isolation or a lack of privacy, and restriction of action or
extreme permissiveness. (Thus *prevention* could be focused on rather
general phenomena in large groups of subjects.)

A detailed discussion of primary and secondary prevention is not
possible here. The identification of some general principles is. Based
on the theoretical model presented (Figure 5-2) and on the non-
specific hypotheses discussed, one may note five principles, or perhaps
more accurately, practices, of prevention:

1. Intervening against psychosocial stressors.
2. Minimizing predisposing and stimulating protective interacting
   variables.
3. Intervention in the area of "mechanisms."
4. Intervention against precursors of disease.
5. Secondary prevention.

While some preventive measures may be non-specifically beneficial
to all individuals and under all or most conditions, in many instances
it is necessary to stipulate the specific context, the particular target
group, and the specific disease entity with which one is concerned.

Much preventive action which is assumed to be beneficial will be
promoted by politicians and health and welfare administrators with-
out waiting for evidence from scientists. Under such conditions this
chapter advocates evaluative research, turning every major social
policy act into a large scale experiment. By making our social system
cybernetic, with feedback loops, our social policies may eventually

become self-corrective so that major hazards originating from expo-
sure of large populations to environmental stressors and/or to well-
meant, but badly founded, social action can be eliminated or at least
modified.

It must be further emphasized that adverse effects upon an
individual's physical or mental health do not *ipso facto* suggest a
need to alter the psychosocial or other stimuli producting this reaction.
It may well be that some ill effects are outweighed by advantages
(economic, social or psychological) for the individual or the collec-
tive community. The balancing of debts and credits is not and can
never be a purely medical affair. It must be subjected to political
assessment. Briefly, then, we must define our criteria as to what to
prevent and why. We must clarify what price we are willing to pay
for disease prevention. On the other hand, decision-makers must
not forget the potential price in their actions which may be paid
in terms of health and well-being.

Finally, in many of today's highly urbanized and industrialized
societies, we tend to forget that efficiency is a means, not an end.
If we are asked to choose between producing more and better goods
at the expense of our social integrity and producing fewer goods of
lower quality, we will unhesitatingly choose the latter if by such
choice we can avoid pain and disaster to our people.

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STRESS AND DISEASE

IN RESPONSE TO EXPOSURE TO NOISE

—A REVIEW

Gösta Carlestam, Claes-Göran Karlsson

and Lennart Levi

STRESS AND DISEASE IN RESPONSE TO EXPOSURE TO NOISE - A REVIEW

Gösta Carlestam, *Claes-Göran Karlsson** and Lennart Levi**

Noise has been defined as any unwanted sound, the most prevalent "waste products" of our age. Numerous authors claim to have shown that noise provokes physiological stress reactions, not only as concomitants to the distress reactions implicited in the very definition of noise, but also through reflex stimulation of the auditory nerves and on to the hypothalamichypophyseal system. It is occasionally claimed that exposure to noise can cause a number of diseases belonging to the field of psychiatry and internal medicine, either by these or by some other mechanisms.

The purpose of this paper is to examine critically the evidence in favor of these hypotheses and to report, in summary, a study conducted at the laboratory for Clinical Stress Research.** At the National Institute of Building Research*, David Wyon and his associates are studying noise as a component in the indoor environment.

Noise and physiological stress

The term "stress" is used here in the sense that Selye described it, namely, the non-specific response of the body to any demand made upon it; a stereotyped, phylogenetically old adaptation pattern primarily preparing the organism for physical activity, e.g. fight or flight.

It is conceivable that in the dawn of the history of mankind, noise very often was a signal of danger or else of a situation requiring muscular activity. In order to survive, the human organism had to prepare itself for activity, inter alia by the non-specific adaptive reaction pattern defined as stress. More often than not, noise in today's industrialized societies has a meaning very different from what it had during stone age. Yet, according to one hypothesis, our genetically determined psychobiological programming still makes us react as if muscular activity would be an adequate reaction to any sudden, unexpected or annoying noise stimulus. True, it can be argued that some authors have demonstrated not an increase but rather no reaction or even a decrease in hormonal activity in response to noise (Bugard, 1955; Sakamoto, 1959). One explanation for this controversy might be that the measurements have been made at varying intervals after noise exposure. Various endocrine systems can react after various intervals or even in different directions, some of the reactions being diphasic. Accordingly, some reactions, present immediately after the exposure, may have disappeared or changed direction in some instances but not in others.

As one may expect, the reaction pattern to noise is not entirely non-specific but is partially conditioned by the specific characteristics of the reacting organism. One man's meat may be another man's poison. Comparing adrenal hormone reactions in response to noise in healthy controls with those of patients with cardiovascular diseases or schizophrenia, Arguelles et al. (1970) found increases in hormone excretion in all three groups, the reactions in the two patient groups, however, being significantly more pronounced.

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Horio et al. (1972) exposed rats to various noise levels, measuring corticosteroid levels in the adrenal glands. They found rapid increases in concentration reaching a maximum after 15 minutes of noise exposure. At *moderate* noise levels, the corticosteroids soon returned to initial levels. At *higher* noise levels, however, corticosteroid concentration remained elevated over longer periods, interfering with the circadian rhythm.

Measuring 17-ketosteroid excretion in urine in response to meaningful and meaningless noise of moderate intensity, Atherley et al. (1970) found that the meaningful but not the meaningless variety did induce physiological stress reactions.

In an experiment conducted at our laboratory, 22 young female IBM operators were studied in their usual work. In half of the group, the noise level produced by their IBM machines increased 6 dB from one day to the next during four consecutive days, the noise levels being 76, 82, 88 and 94 dB–C, respectively. The other half were subjected to the same noise levels but in the opposite order (i.e., 94, 88, 82, and 76 dB–C, respectively). The noise level normally prevailing in the office was 76 dB–C. Every working day started with two hours of rest without noise exposure, followed by three 2-hour work periods with noise exposure as indicated.

Contrary to what might be expected, the subjects reported only minor increases in self-rated fatigue (figure 1) and "distress" (figure 2). Although these ratings increased slightly with increasing noise, the rating differences between the highest and lowest noise levels were conspicuously small. The corresponding epinephrine and norepinephrine excretion levels (figures 3 and 4) were low or moderate and the changes from control to noise periods and from low to high noise levels were usually non-significant. Thus, not even the objectively rather considerable noise levels used were particularly potent as stressors. This may be due to the familiarity of the noise and to the generally positive attitudes of these subjects to the job per se and to the experiment. It is conceivable that such factors may have counteracted the stressor effects of the noise. Briefly, then, noise may be a potent stressor under some circumstances and in some individuals, but need not generally be so.

Noise and disease

Sakamoto (1959) found that more than 50%–i.e. a rather high proportion–of the inhabitants living close to an airport complained of various types of somatic distress, possibly induced by the aircraft noise.

In epidemiological studies, several authors (Mjasnikow, 1970; Andriukin, 1961; Shatalov et al., 1962; Ratner et al., 1963) report an increased incidence of *hypertension* in workers exposed to high noise levels. According to Mjasnikov, this increase in morbidity manifests itself after 8 years of exposure, reaching a maximum after 13 years of exposure.

Similarly, other authors (Jerkova and Kremarova, 1965; Andrukovich, 1965; Strakhov, 1966; and Dumkina, 1970) found an increased incidence of "nervous complaints" in workers habitually exposed to higher noise levels. Living in areas close to a noisy airport was accompanied by increased number of admissions to psychiatric hospitals (Abey-Wickrama et al., 1969 and 1970). However, the causal implications of this statistical relationship can be seriously questioned (Chowns, 1970).

Jensen and Rasmussen Jr. (1970) inoculated mice with various infectuous agents, before or after exposing them to noise. It was found that those inoculated with stomatite
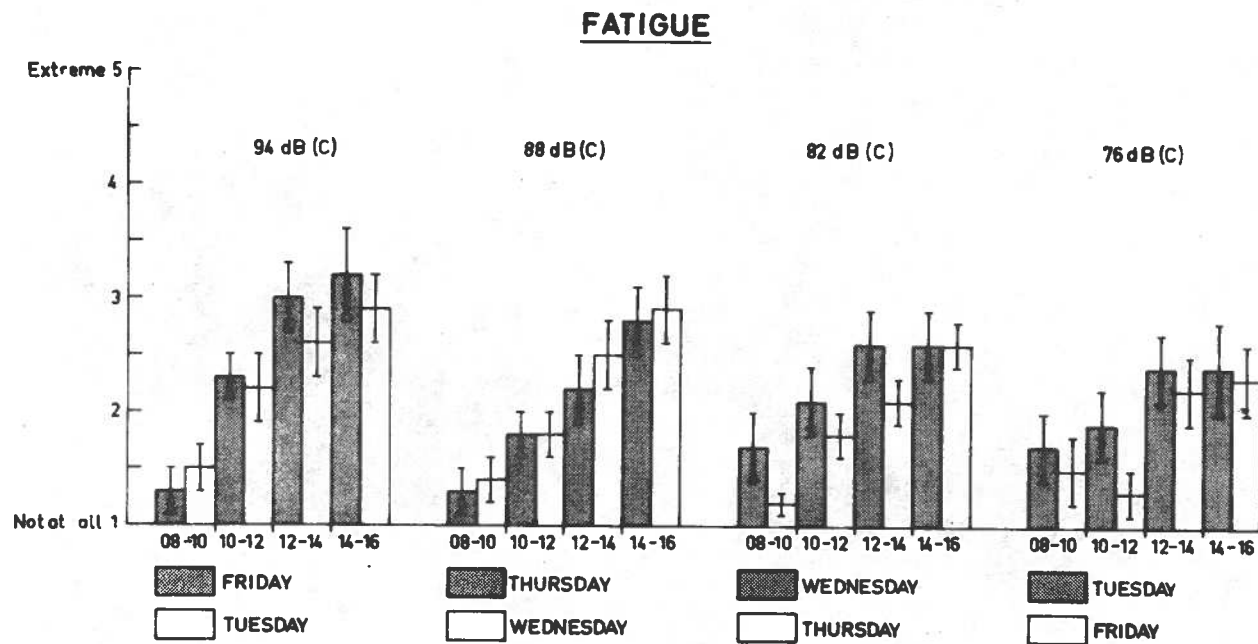
Figure 1. Self-rated "fatigue" under different noise conditions and during different times of the day.
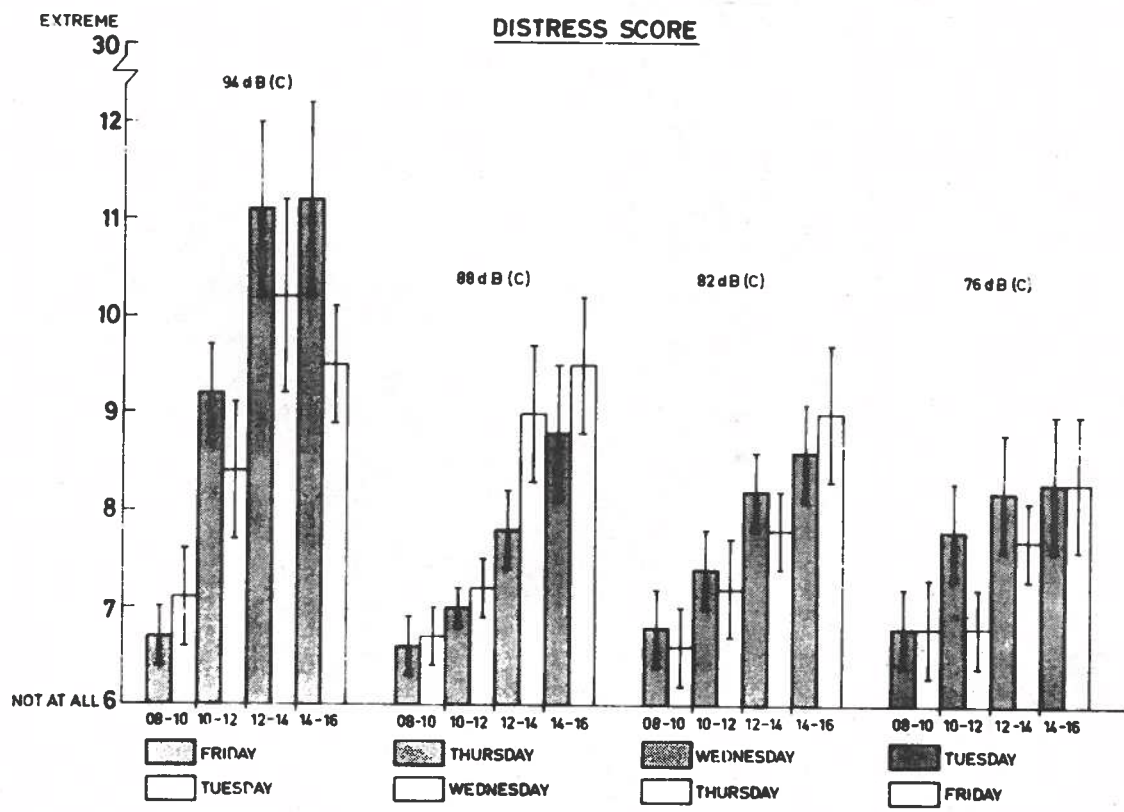
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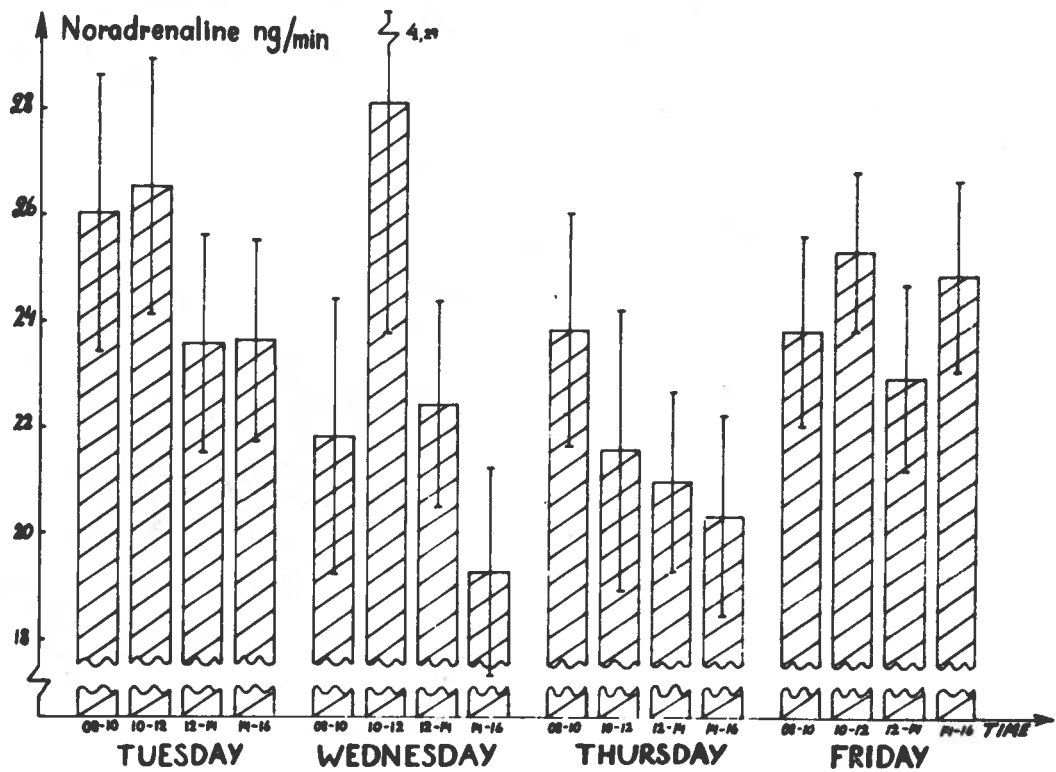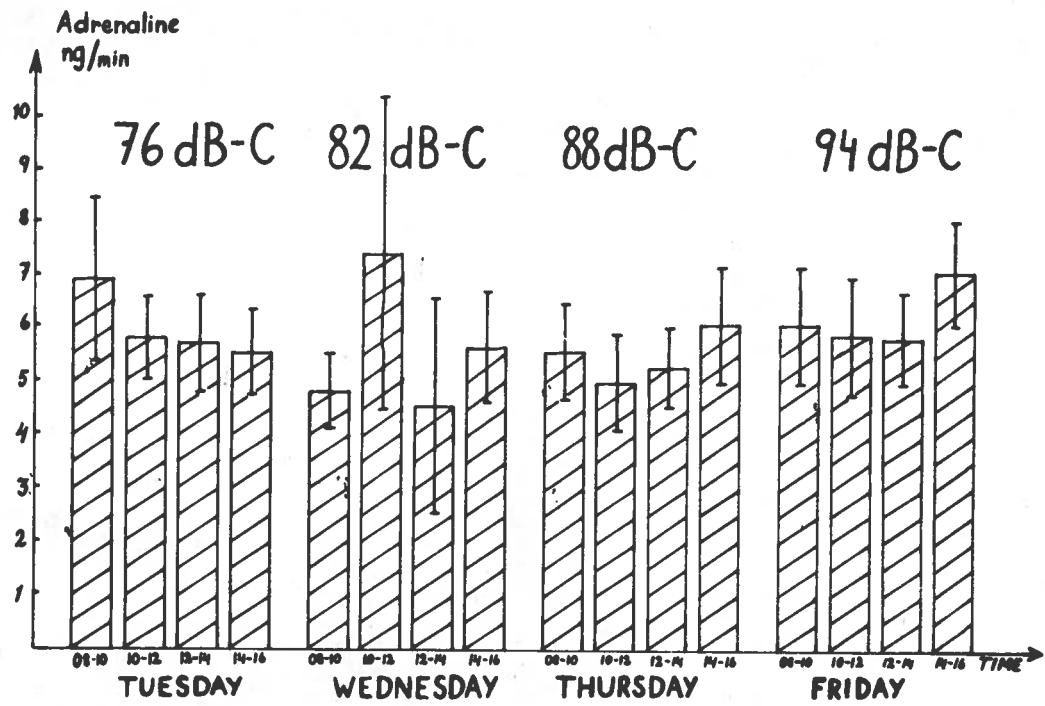Figure 2. Self-rated "distress" under different noise conditions and during different times of the day.

Figure 3. Urinary excretion of adrenaline and noradrenaline during four consecutive days with increasing noise level.
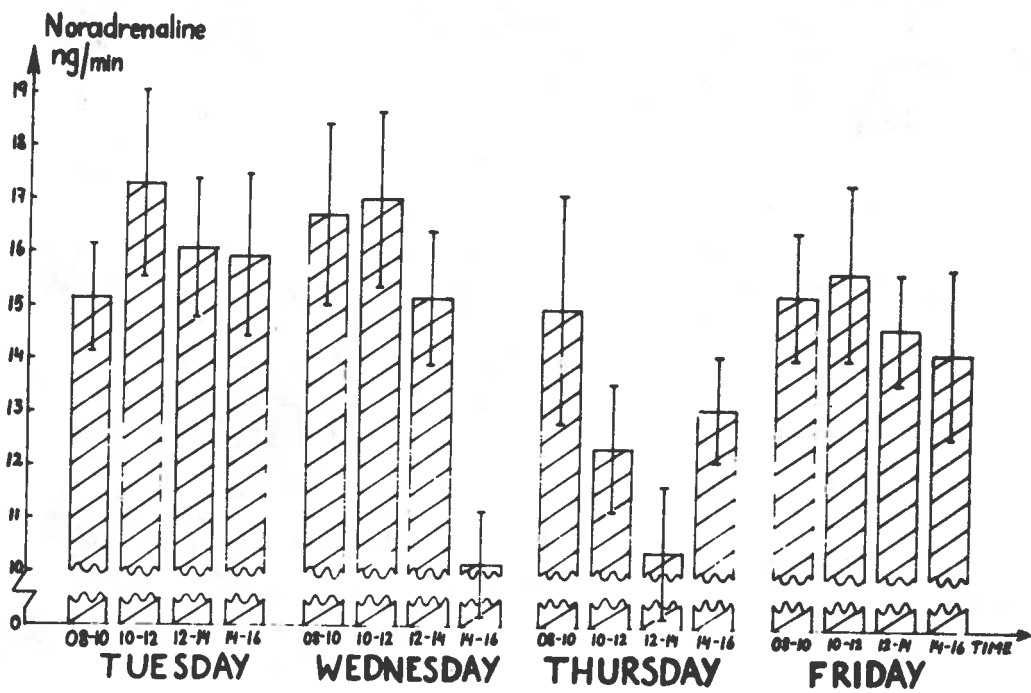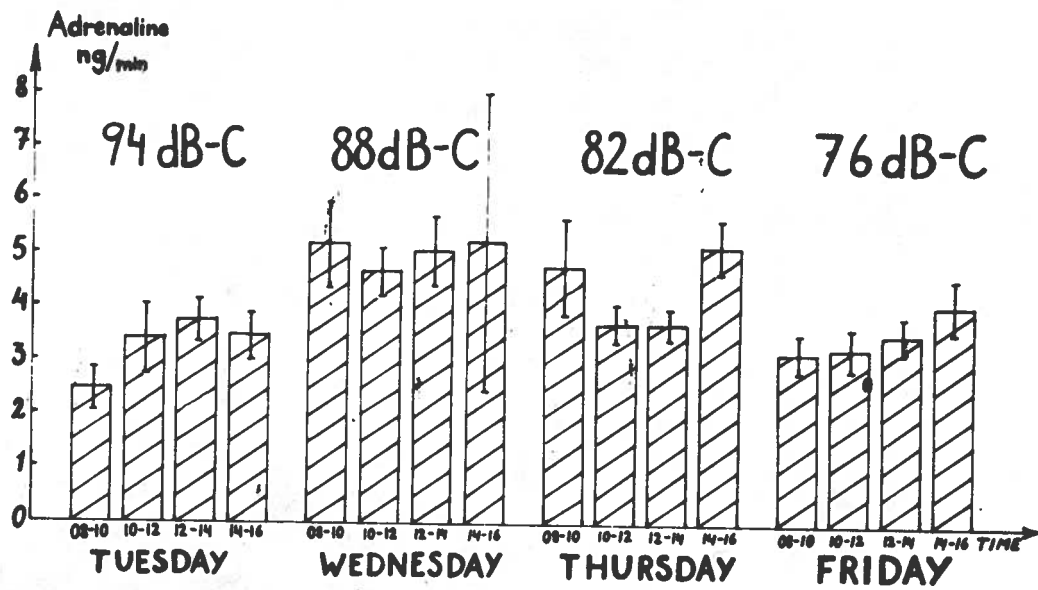
Figure 4. Urinary excretion of adrenaline and noradrenaline during four consecutive days with decreasing noise level.

virus just *before* noise exposure were *more* susceptible, whereas those inoculated *after* the exposure were *less* susceptible, than non-exposed controls.

Reviewing studies on noise and mental disease, Lader (1971) concludes that noise exposure does not generally increase psychiatric morbidity but might be of some etiologic significance in neurotic and anxious subjects.

Briefly, then, some of the physiological reactions found in response to noise exposure seem to be closely related to the non-specific physiological reaction pattern defined as "stress". Stress has been hypothesized to be one of several pathogenetic mechanisms acting by increasing the "rate of wear and tear" in the organism. Although some circumstantial evidence has been presented, there is still no proof.

Some epidemiological studies seem to indicate a higher occurrence of "psychosomatic" and mental disorders in subjects exposed to prolonged and rather intense noise. However, it should be kept in mind that such an exposure is often accompanied by exposure to a variety of *other* potentially noxious stimuli. In addition, various segregational forces may "sort out" particularly susceptible individuals to noisy, unpleasant and/or pathogenic environments.

Accordingly, we have to conclude that the evidence in favour of noise as a major pathogenetic environmental agent is rather shaky. To solve this controversy, future research should focus on controlled intervention studies with an interdisciplinary and multifactorial design.

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Plenary Session 11

A synopsis of ecology and psychiatry: Some theoretical psychosomatic considerations, review of some studies and discussion of preventive aspects

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INTRODUCTION

The argument that environmental *physical* stimuli cause disease is well established for a large number of factors and diseases. It is well known that exposure, avoidance or manipulation of these factors increases, decreases or removes the likelihood of becoming ill or reverses ill-health when it occurs.

The role of extrinsic, *psychosocial* stimuli is not so clear. This paper is an attempt to discuss ecology and psychiatry, first focusing on theoretical etiological and pathogenetic aspects of psychosomatic disorders, then illustrating these aspects with data from recent studies, and finally presenting some viewpoints on prevention (Kagan and Levi, 1971).

According to Seyle (1971), stress is the non-specific response of the body to any demands made upon it (cf. also Levi, 1972). The intensity and duration of this stereotyped, phylogenetically old adaptation pattern, primarily preparing the organism for physical activity, e.g. fight or flight, is assumed to be closely related to the rate of wear and tear in the organism and, consequently, eventually to an increased morbidity and mortality, not in any specific disease but in a *variety* of diseases. In other words, if environmental changes occur frequently and/or are of great magnitude, and/or if the organism is vulnerable, generally or with respect to some particular organ or organ system, e.g. due to genetic factors or previous environmental influences, the physiological stress reactions usually increase in intensity and duration (cf. Fig. 1).

Clinically manifest symptoms may appear even at relatively low stress levels, namely if the subject pays much attention to, or misinterprets, the proprioceptive signals originating from such reactions, as in the case of hypochondriasis. At higher stress levels, almost all subjects experience these signals as unpleasant. Sometimes they are detrimental to the *function* of the organism, as in the case of organ neuroses. If such reactions are particularly prolonged, or often repeated, it has been claimed that they may eventually even lead to *structural* damage. As to this last step, there is a high level of suspicion, but no proof.
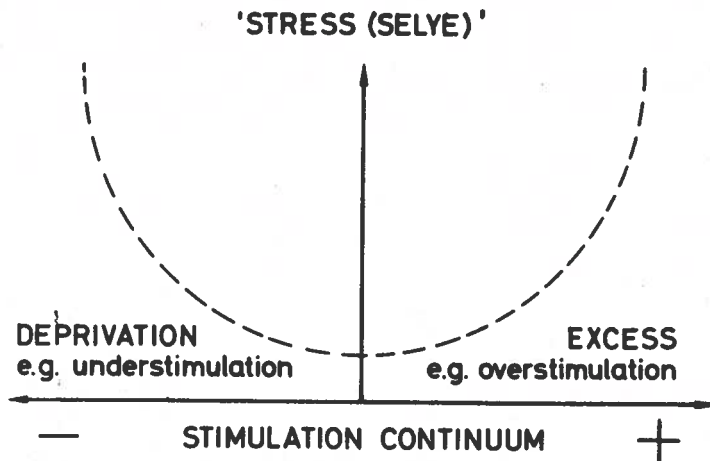
FIG. 1   *Theoretical model of the relation between physiological stress as defined by Selye and various levels of stimulation. According to this hypothesis, deprivation of stimuli as well as excess is accompanied by an increase in 'stress (Selye)' (Levi, 1972).*
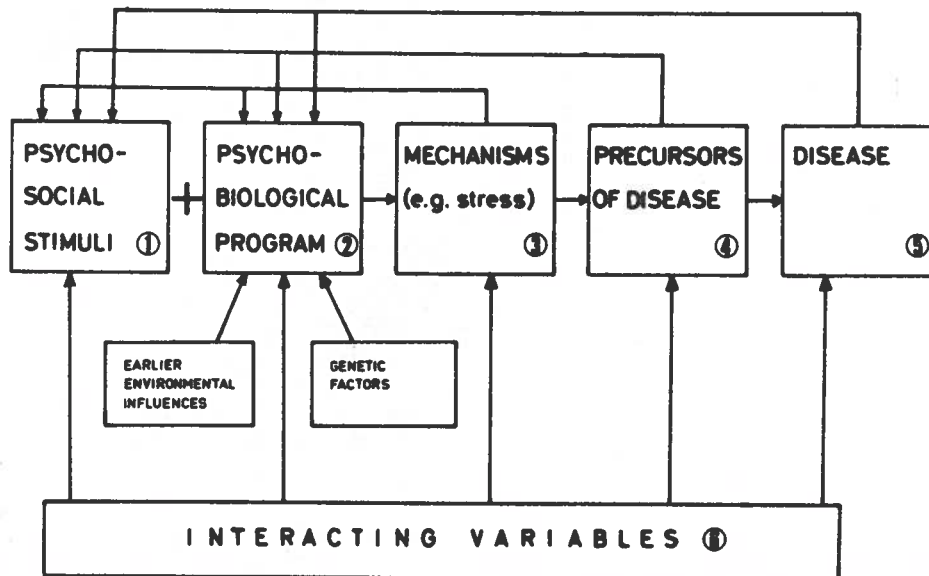

FIG. 2   *A theoretical model of psychosocially mediated disease. The interaction between psychosocial stimuli (1) and the psychobiological program (2) determines the psychological and physiological reactions [mechanisms (3), e.g. stress] of each individual. These may, under certain circumstances, lead to precursors of disease (4) and to disease itself (5). This sequence of events can be promoted or counteracted by interacting variables (6). The sequence is not a one-way process but constitutes part of a cybernetic system with continuous feedback (Kagan and Levi, 1971).*

NON-SPECIFIC ETIOLOGY

Let us now examine some of the main hypotheses in the field of ecology and psychiatry (cf. Fig. 2).

The main hypothesis reads that psychosocial stimuli can cause disease. The etiology can be specific, i.e. specific disease is caused by specific stimuli or in subjects with certain constitutional characteristics. The etiology can also be non-specific, i.e. disease will occur in response to a wide variety of stimuli, and/or in a wide variety of subjects.

Let us, in the present context, focus on the *non-specific* etiology and discuss here some hypotheses concerning non-specific etiology of psychosocially mediated disease: (1) Most (or all?) life changes evoke in most (or all?) subjects a stereotyped, phylogenetically old, adaptational pattern of responses ('stress [Selye]'), generally preparing the organism for fight or flight. (2) 'Stress (Selye)' is characterized by increased activity in the hypothalamo-sympathoadrenomedullary, hypophyseo-adrenocortical and possibly thyroidal systems. (3) The reactions, at least if prolonged, intense or often repeated, are accompanied by an increased rate of wear and tear in the organism. (4) Such generally increased rate of wear and tear leads in the long run to increased morbidity and mortality in various diseases.

PSYCHOSOCIAL STIMULI, PATHOGENIC MECHANISMS AND DISEASE

Let us now review some recent evidence supporting these hypotheses.

Psychosocial stimuli lasting some *hours* increase 'stress (Selye)'. This is reflected in increases in, e.g., adrenaline and noradrenaline excretion, and in plasma 17-hydroxy-corticosteroids, free fatty acids and triglycerides (see Figs. 3 and 4) (Carlson et al., 1972).

Psychosocial stimuli lasting several *days* increase 'stress (Selye)'. This is reflected in, e.g., adrenaline excretion (see Fig. 5), in plasma free fatty acids, triglycerides, cholesterol (Fig. 6), protein-bound iodine (Fig. 7) and fibrinolysis (Fig. 8), and in ST and T depressions in the ECG pattern (cf. Fig. 9) (Levi, 1972).

Psychosocial stimuli lasting *weeks* and *months* increase 'stress (Selye)'. A longitudinal study has demonstrated a significant, positive correlation between the weekly sum of 'life change units' (cf. Rahe, 1972) and adrenaline excretion during the days prior to interviews (Theorell et al., 1972). The 3 studies cited above all support our hypothesized relationship between psychosocial stimuli (Fig. 2, box 1) and potentially pathogenic mechanisms (Fig. 2, box 3).

Psychosocial stimuli (life changes measured according to Rahe) precede increased morbidity and mortality in a *variety* of diseases, psychiatric as well as somatic. This has been shown in a number of studies (cf., e.g., Theorell, 1970; Rahe, 1972; Brown et al., 1972a,b; Paykel and Uhlenhuth, 1972), thus supporting the hypothesized relationship between psychosocial stimuli and disease (Fig. 2, boxes 1 and 5).

Increased levels of triglycerides and cholesterol do predict increased risk not only for subsequent ischemic heart disease (cf. Keys, 1970) but also for a variety of other diseases, as found by Tibblin in a large-scale prospective study on males born in 1913 and followed annually since 1963, i.e. for 9 years (see Figs. 10 and 11). These findings support the hypothesized relationship between mechanisms and disease (Fig. 2, boxes 3 and 5).

Various diseases have been induced experimentally in animals, including primates, by exposure to psychosocial stressors. In this way, several authors have induced degenerative heart disease and high blood pressure (Lapin and Cherkovich, 1971; Brady, personal communication), and peptic ulcer (cf. Rioch, 1971), supporting the hypotheses of psy-
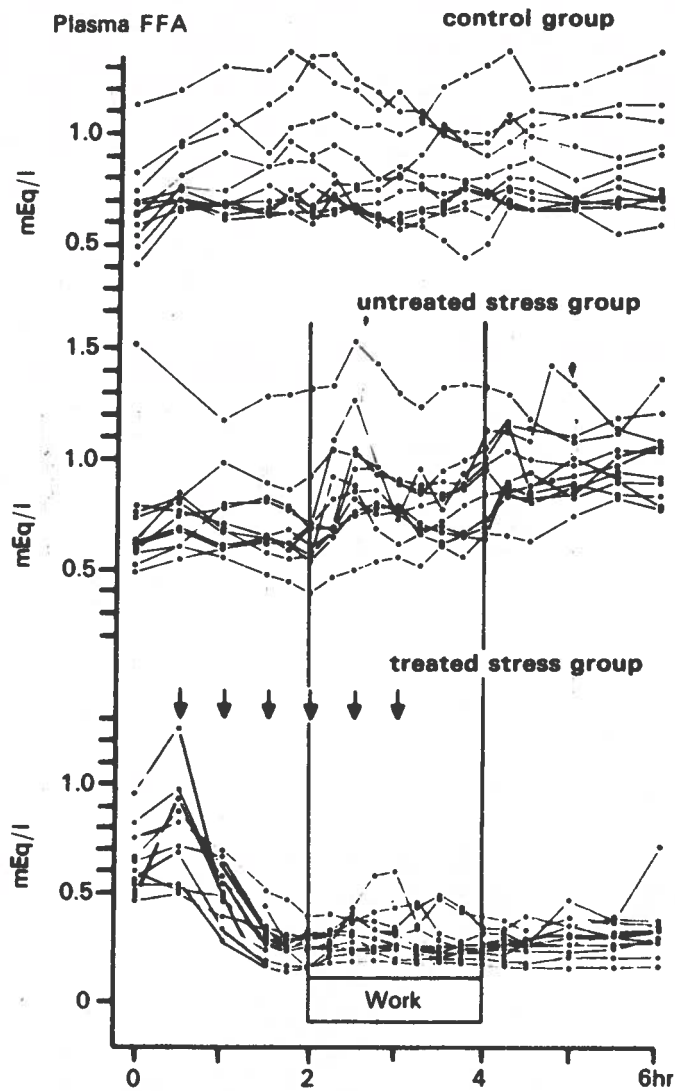
FIG. 3   *Individual values for arterial plasma levels of free fatty acids (FFA) in the control group (top), the untreated stressor-exposed group (center) and the treated stressor-exposed group (bottom). Arrows indicate nicotinic acid administration (0.5 g 6 times, i.e. every 30 min in the treated stressor-exposed group) (Carlson et al., 1972).*

chosocial stimuli as possible etiological agents in a variety of diseases (cf. Fig. 2) (for a review, see Levi, 1971).

From this, we may *conclude* that psychosocial laboratory and real-life conditions may provoke marked, stereotyped changes in bodily function (mechanisms). These changes include increases in catecholamine excretion and in plasma levels of free fatty acids, triglycerides, cholesterol and protein-bound iodine, and a decrease in serum iron and
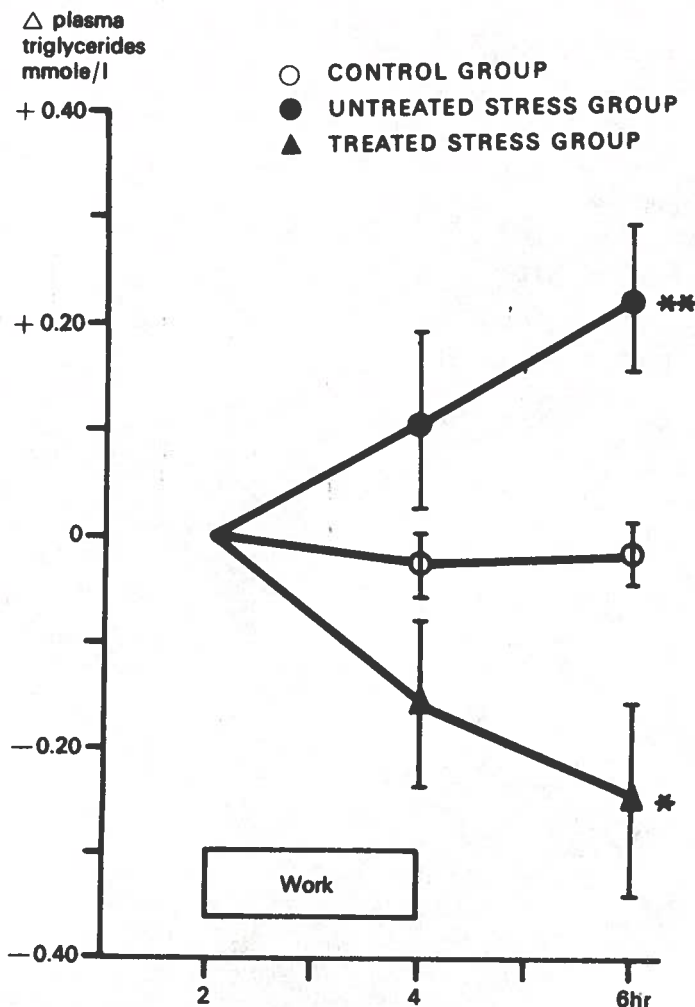
FIG. 4   *Mean ± standard error of the mean for the changes in plasma triglycerides during and after the second 2-hour period (cf. Fig. 3), which was designed to induce distress in the untreated and treated stressor-exposed groups but not in the control group (Carlson et al., 1972).* * p < 0.05, ** p < 0.01.

fibrinolysis. The increased catecholamine output, occurring in response to almost any type of environmental change and being positively correlated *inter alia* to the intensity of self-reported distress, is thought to be part of a general potentially pathogenic mechanism (for discussion, see Levi, 1972).

It has further been shown that subjects exposed to frequent and dramatic environmental changes run a higher risk of developing myocardial infarction within the next 6 months (Theorell, 1970). Similar relationships have been demonstrated for *other* diseases, including psychiatric disorders (see review by Rahe, 1972).

Finally, it has been found that high triglyceride and cholesterol levels in a non-selected population are positively related to a subsequent increase in mortality, not only in myocardial infarction but in other diseases as well.
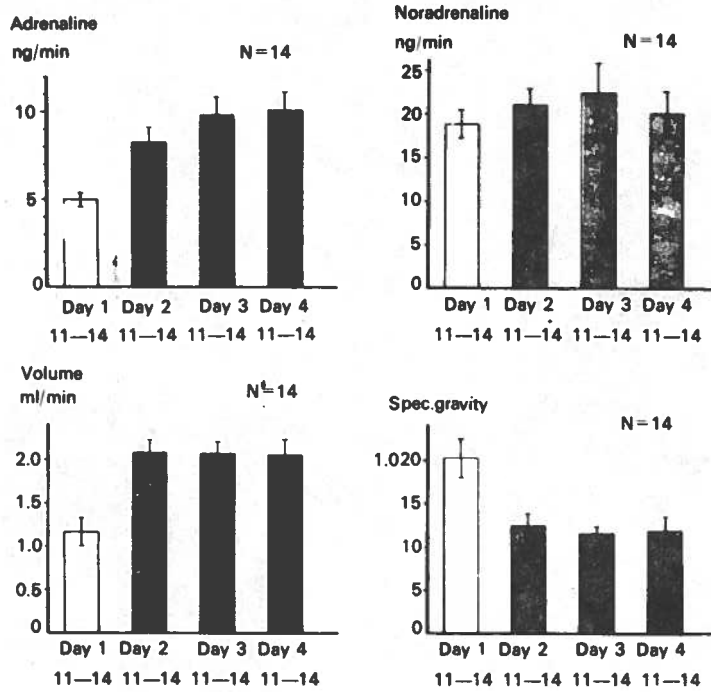
FIG. 5   Urinary adrenaline and noradrenaline excretion, urine flow and specific gravity during control conditions (empty bars) and corresponding periods of days 2, 3 and 4 of a stressful 72-hour vigil, at 11—14 hours (Levi, 1972). Means ± SEM.
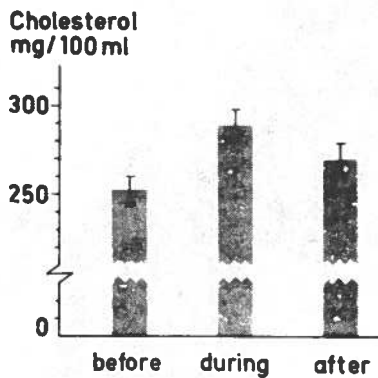

FIG. 6   Plasma cholesterol in 32 army officers 24 hours before the start of a stressful 72-hour vigil, 24 hours after the start and at the end (72 hours after the start). Means ± standard errors.
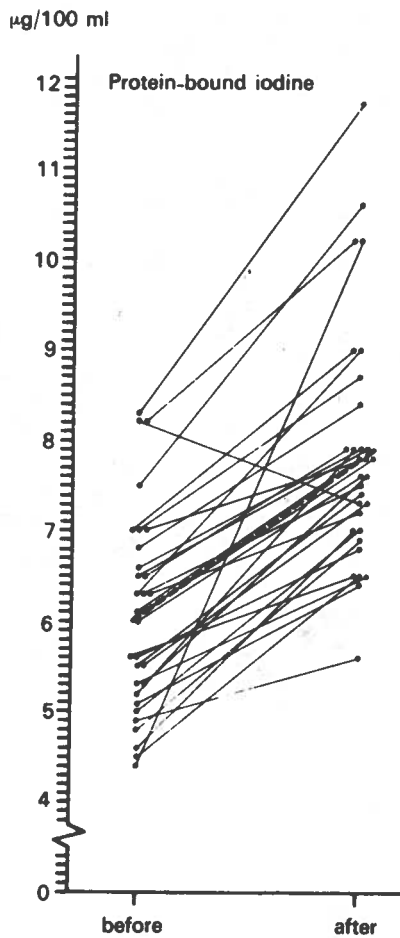
µg/100 ml

FIG. 7   *Protein-bound iodine before and after a 72-hour vigil (Levi, 1972).*
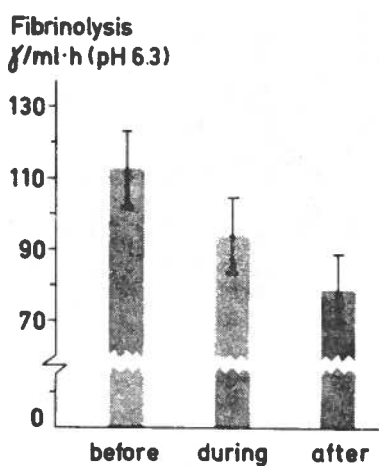
Fibrinolysis
ɣ/ml·h (pH 6.3)

FIG. 8   *Fibrinolysis in 32 army officers 24 hours before the start of a stressful 72-hour vigil, 24 hours after the start and at the end. Means ± standard errors.*
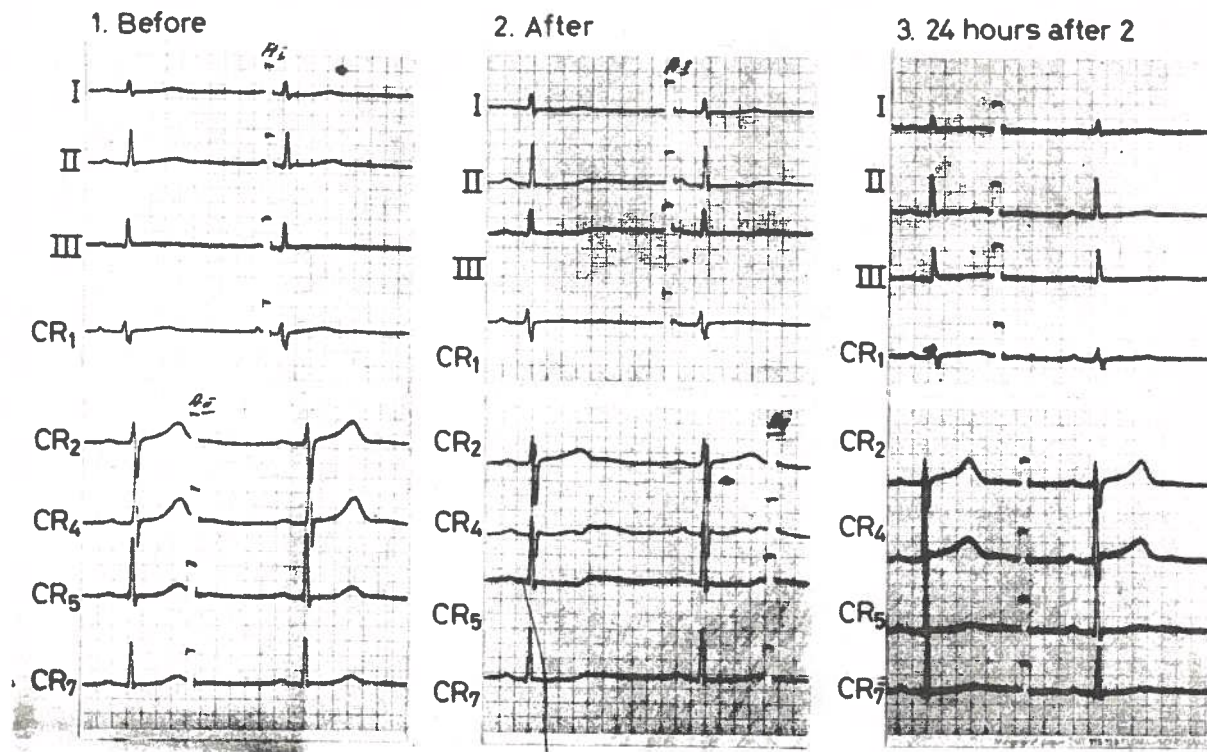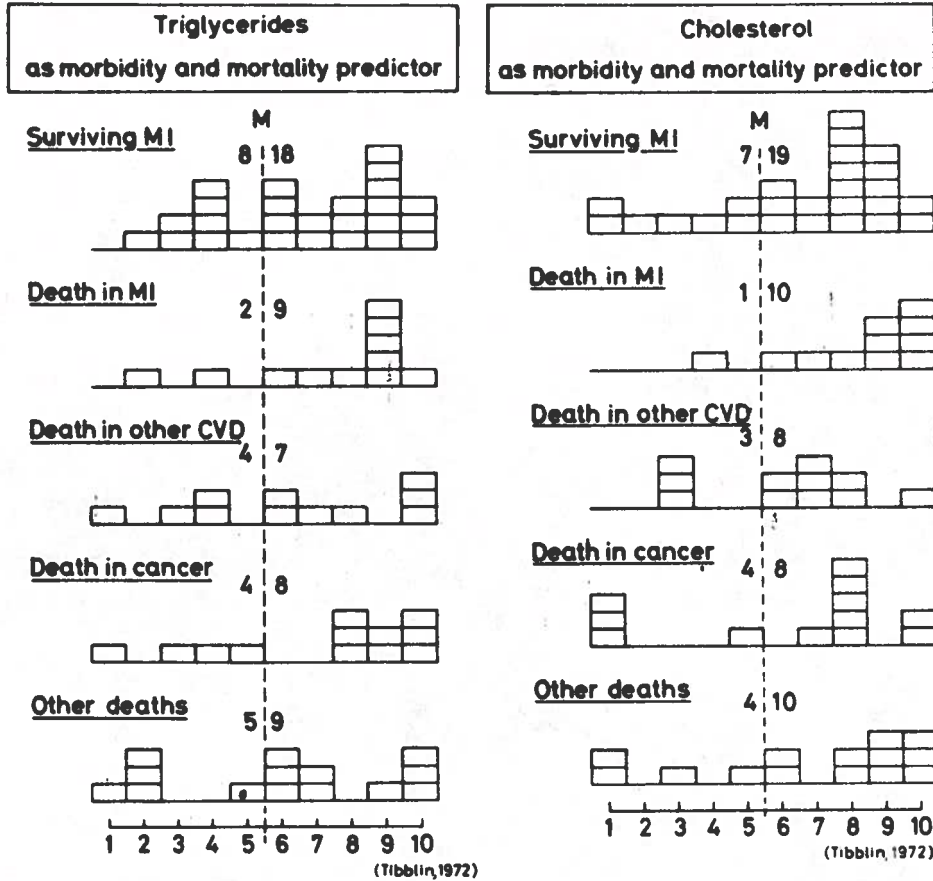
FIG. 9   *ECG at rest of a middle-aged army officer, 24 hours before the start of a stressful 72-hour vigil, at the end and 24 hours later. Note reversible ST and T changes in lead CR$_5$.*

L. LEVI AND A. KAGAN

FIGS. 10 *Plasma triglycerides and cholesterol registered in 1963 as predictors of subsequent morbid-*
and 11 *ity and mortality in myocardial infarction (MI), and of mortality in other diseases. Distribu-*
tion in deciles (1–10) of plasma levels in relation to deaths. Vertical line indicates medians.
Each box indicates one death or case of illness. Figures indicate distribution of below-
median (left) and above-median (right)triglyceride and cholesterol levels (Tibblin, personal
communication). Above-median levels seem to predict subsequent morbidity and mortality
not only in MI but also in other cardiovascular diseases (CVD), cancer and other disorders
(Levi, 1972).

Taken together, these data demonstrate the relative importance of non-specific factors
in the etiology and pathogenesis of a variety of diseases. This does not mean that specific
factors are unimportant but that non-specific factors deserve more study, particularly in
relation to various psychiatric and 'psychosomatic' diseases of multiple etiology.

PRINCIPLES OF MONITORING AND PREVENTION

Since our knowledge of psychosocial hazards and disease is so incomplete, much of what
we say about *monitoring* for and preventing disease is speculative. Changes likely to
expose large numbers of people to new social relationships or generally necessitate many
major adaptations should alert administrators to the possibility of subsequent health

hazards (cf. Kagan and Levi, 1971). Awareness of this possibility may be generated at national, regional and local levels, or in a smaller group such as a factory or enterprise. If the change is likely to be accompanied by removal from old forms of social support and either lack of, or failure to use, new forms, there will be a need for preventive action. Awareness of possible psychosocial hazards in a municipality may arise from an examination of mortality and morbidity records. Such data are not likely to be conclusive in any way, but high and/or rapidly increasing rates for suicide, neuroses and psychosomatic disorders would invite more detailed enquiry. Another somewhat speculative source of 'warning' data might be juvenile delinquency rates, which may focus enquiry on a district, a class of people, a school or a family. *Prevention* could perhaps be focused on rather *general* phenomena in large groups of subjects, namely *deprivation* or *excess* of a large number of stimuli like (a) understimulation and overstimulation, (b) lack of parental care, and overprotection, (c) poverty and affluence, (d) lack of contact and lack of privacy, (e) restriction of action and extreme permissiveness etc. (cf. Fig. 1).

Space does not allow anything like a detailed discussion of primary and secondary prevention. Let us just mention some very general principles, based on the theoretical model presented and on the non-specific hypothesis previously discussed.

The principles of prevention are: (a) intervene against psychosocial stressors, (b) minimize predisposing and promote protective interacting variables, (c) intervene in mechanisms, (d) intervene against precursors of disease, and (e) secondary prevention.

Some preventive measures may be non-specifically beneficial, i.e. in all (or most) individuals and under all (or most) conditions. In other cases, probably in most, it is necessary to stipulate the specific context, the specific group and the disease entity. For obvious reasons it is impossible to present, within a single paper, the endless variety of specific programs one might want to consider.

PRINCIPLES OF RESEARCH

Needless to say, our widespread and profound lack of knowledge in this field necessitates research. Kagan and Levi (1971) have recently proposed that at the present stage the following hypotheses are ripe for testing: (a) Control of psychosocial environment (Fig. 2, box 1) reduces disease. (b) Control of psychological and/or physiological reaction (Fig. 2, box 3) reduces disease. (c) These responses are interrelated and are mediated through neuroendocrine mechanisms as a final common pathway.

Much presumably beneficial preventive action will be promoted by politicians and health and welfare administrators without waiting for evidence from scientists. Under such conditions we advocate evaluative research, turning every major social policy act into a large-scale experiment. By making our social systems cybernetic, with feedback loops, our social policies may eventually become self-corrective, so that major hazards originating from exposure of large populations to environmental stressors and/or to well-meant but badly founded social action can be eliminated or at least modified.

It must further be emphasized that possible ill-effects in relation to an individual's physical or mental health do not automatically make psychosocial or other stimuli a target for preventive action. It may well be that some of these ill-effects are outweighed by short- or long-term advantages (economic, social or psychological) for the individual or the collective, e.g. prosperity, wealth. The balancing of debits and credits is not and can never be a purely medical affair but must be subjected to political assessment. Briefly, then, we must define our criteria as to what to prevent and why, and to clarify what price we are willing to pay for disease prevention, e.g. in social or economic terms. Similarly, in their attempts to achieve affluence and social progress, decision makers should not forget the potential price to be paid in terms of health and well-being.

In many of today's highly urbanized and industrialized societies, we often tend to forget what has been emphasized by a Chinese author, namely that 'efficiency is a means, not an end. If we are asked to choose between producing more and better goods at the expense of our social integrity and producing fewer goods of lower quality, we will unhesitatingly choose the latter if by such choice we avoid pain and disaster to our people.'

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