BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 17 1947

OXYGEN POISONING IN MAN

BY

KENNETH W. DONALD, *D.S.C.*, M.D., M.R.C.P.

Late Senior Medical Officer, Admiralty Experimental Diving Unit; Chief Assistant, Medical Professorial Unit, St. Bartholomew's Hospital

PART I

The recent war greatly stimulated the study of human tolerance to various changes in environment. This article confines itself to tolerance to increased tensions of oxygen, though there are other important factors at increased pressures which are not considered here. At sea-level there is an oxygen tension of about 159 mm. of mercury, and this is the maximum oxygen tension encountered in any natural environment. The oxygen tension in the tissue spaces of warm-blooded animals is from 20 to 40 mm. of mercury. In under-water work man, by means of various appliances, breathes gases at the pressure to which he is exposed, this being the first essential of prolonged under-water existence. The second essential is that his respiratory movements must continue within their normal range and with their normal frequency. The third is that the gases to which he is exposed must not be noxious, either at the time of exposure or on returning to normal atmosphere. Under most operational conditions it is preferable that the diver is self-dependent and carries his respiratory gases with him. If he carries air, then this must be expelled from his apparatus after each breath and there is great wastage and exposure to dangerous tensions of nitrogen. If he carries oxygen, this gas can be employed not only for metabolic purposes but for the essential rinsing of the lungs during respiratory movement. Thus no gas is wasted and maximum endurance for a minimum load is possible. It would appear, therefore, that oxygen is the ideal gas for this purpose, provided it is devoid of toxic effects. It is almost certain that the tissues of man, when breathing oxygen at increased tensions, are exposed to an internal environment which has been previously unknown to living matter, and it is therefore difficult to postulate what the reaction to such tensions would be. Whales, in deep dives, protect their general tissues by the complete collapse of their relatively small lungs and transfer of the gases to the inactive dead space.

The first important contribution to this subject was made by Paul Bert in 1878. His pioneer work has withstood the test of time in a most impressive manner. He showed that oxygen at increased pressures was highly poisonous and that no living matter was exempt. Larks exposed to 15–20 atmospheres of air convulsed and finally died. In a large series of experiments Bert showed that the oxygen tension was the decisive factor in the immediate effect of air or of any mixture of nitrogen and oxygen. Lorrain Smith (1899) next demonstrated that animals breathing oxygen at moderately high tensions over prolonged periods suffered severe and finally fatal pulmonary damage. An enormous amount of animal experimentation followed, but "L'effet Paul Bert" (convulsant) and "L'effet Lorrain Smith" (pulmonary irritation) remained the cardinal features of oxygen poisoning.

With regard to human experiments, the first recorded were by Bornstein and Stroink (Bornstein, 1910; Bornstein and Stroink, 1912), who breathed oxygen for 45 minutes at 3 atmospheres absolute (ats. abs.) in the Elbe tunnel without ill effect. In 1912 Bornstein suffered from clonic spasm of the legs while riding an ergometer under similar conditions for 51 minutes. In 1930 the late Dr. J. S. Haldane (Haldane and Priestley, 1935) reported confusion and amnesia in deep-sea air divers at 300 ft. (91.4 m.), and these symptoms were attributed to the raised tension of oxygen. These effects were proved by Behnke *et al.* (1935) to be due to the intoxicant effect of nitrogen at high pressures. Yet as a result of this misconception diving on pure oxygen was limited in the Royal Navy to 2 ats. abs. (apart from submarine escape). In 1933 two Royal Naval officers, Damant and Phillips, breathed oxygen at 4 ats. abs. in compressed air. Convulsive symptoms occurred in 16 and 13 minutes respectively. Phillips suffered a major convulsion after being turned on to air but while still at 4 atmospheres pressure (Thomson, 1935). In 1934–6 Behnke and co-workers carried out a series of human experiments. Only two exposures were made at 4 atmospheres, where one subject suffered acute syncope after 43 minutes. The other subject convulsed after 44 minutes. At 3 atmospheres four subjects breathed oxygen for three hours with no demonstrable ill effect. In a second series at this pressure the experiment was continued into the fourth hour, when three subjects suffered abrupt onset of vertigo, nausea, and a sensation of impending collapse. Concentric contraction of the visual field was also demonstrated. These results were published and obtained widespread recognition and acceptance. Throughout the world it was assumed that men at comparative physiological rest, as in these experiments, were safe breathing oxygen for at least 30 minutes at 4 atmospheres, and for at least three hours at 3 atmospheres. In time even the proviso concerning rest was usually omitted. The British finding appeared to have

been unnoticed, or forgotten, even in Great Britain. In 1941 J. B. S. Haldane reported a convulsion after breathing oxygen for under five minutes, at a pressure of 7 ats. abs., during experiments related to the *Thetis* disaster.

The investigations of oxygen poisoning described here were started in April, 1942, owing to the occurrence of several cases of unconsciousness in oxygen-breathing apparatus at depths and in times which were then considered to be safe. The Admiralty Experimental Diving Unit was created to investigate this and other urgent problems of high-pressure physiology. The main body of human experiments described in this article were carried out between June, 1942, and February, 1943. No experimental dives where men had breathed pure oxygen at toxic tensions under water had yet been reported. The object of these experiments was to gain a more comprehensive picture of oxygen poisoning in the human. Large groups of subjects were therefore employed, and over 2,000 experiments were carried out. Great care was taken to avoid an heroic or "Jules Verne" atmosphere.

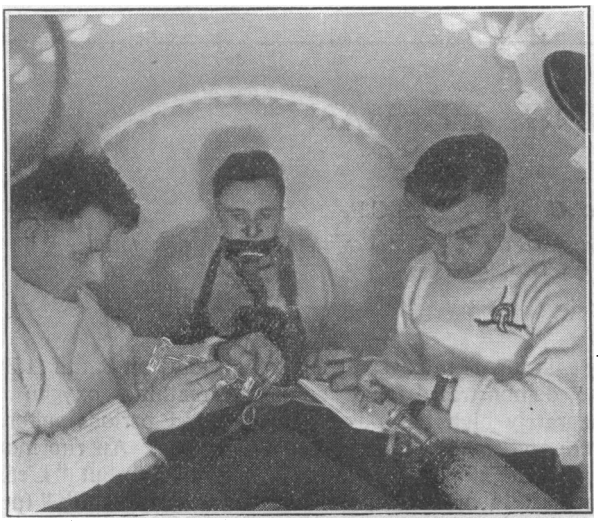

FIG. 1.—Subject breathing oxygen under pressure.

FIG. 2.—Soft-helmeted counter-lung oxygen-diver. (Human torpedoes.)

[Admiralty Photos.

The Marked Variation of Oxygen Tolerance in Man

The first series of experiments to be carried out was to determine the oxygen tolerance of a group of healthy male subjects at a fixed oxygen tension (3.7 ats. abs.). This series was carried out in a pressure chamber of 100 c. ft. (2.83 m.^{3}) capacity. The subject was seated opposite two observers who were in telephonic communication with those outside. All subjects breathed oxygen at pressure until acute symptoms occurred. Experiments in compressed air have a number of advantages. The subject's state can be easily observed and subjective end-points are less likely. Convulsions are a lesser risk. Oxygen was breathed from a Siebe Gorman "salvus" apparatus. Efficient rinsing out of the subject's lungs was carried out and repeated frequently. A series of analyses, however, showed that even with this regime it was difficult to maintain a concentration higher than 95% of oxygen. In most exposures the pulse and respiratory rates were noted every five minutes. Subjects varied from cooks to recently trained divers, experienced divers, submarine ratings, medical officers, special service operational personnel, and mine-disposal officers and ratings. All were Grade A1 in fitness, and ages varied from 18 to 40 years. Experiments carried out in this manner are referred to hereafter as in the "dry," in contrast to those carried out under water and referred to as in the "wet." The results of these experiments are given in Table I and shown graphically in Fig. 4 (in the "dry").

TABLE I.—*Oxygen Poisoning at 90 ft. (27.4 m.) in the Dry in 36 Subjects in Order of Performance*

Exposure (mins.)	Symptoms	Exposure (mins.)	Symptoms
96	Prolonged dazzle; severe spasmodic vomiting	18	Vertigo and severe lip-twitching
67	Severe lip-twitching	18	Vertigo + +; epigastric aura
62	Euphoria and lip-twitching	17	Lip-twitching
62	Nausea and vertigo; arm twitch	17	Lip-twitching; spasmodic respiration
54½	Severe lip-twitching	17	Lip-twitching; spasmodic respiration
51	Dazzle and lip-twitching		
50½	Blubbering of lips; fell asleep	16¼	Slight lip-twitching
50½	Dazed and lip-twitching	16	Severe lip-twitching; spasmodic respiration
34½	Nausea, vertigo, lip-twitching	15½	Inspiratory predominance; lip-twitching and syncope
33	Convulsed		
32	,,	15	Nausea, syncope, and confusion
32	Severe lip-twitching		
30	Convulsed	14	Lip-twitching
26½	,,	12½	,,
25½	Drowsiness and lip-twitching	9	Dazed and lip-twitching; paraesthesiae
24½	Severe lip-twitching	9	Lip-twitching and vertigo
23	Lip-twitching; epigastric aura	7½	Severe lip-twitching
		7	"Diaphragmatic spasm"
20½	Lip-twitching; twitch L. arm; amnesia	6	Severe nausea
		6	Severe lip-twitching
19½	Convulsed		

Out of 36 subjects five convulsed, the rest recovered on being turned on to air. The most striking finding was the enormous variation in oxygen tolerance in a group of human beings. Exposures causing marked symptoms at this tension varied from 6 to 96 minutes. The tolerance of each subject was unpredictable. Many attempts to correlate tolerance with age, height, weight, physical fitness, athleticism, smoking, ingestion of alcohol, psychological health, or personality assessments all failed. Symptoms will be discussed in detail later.

The times of exposure causing acute symptoms show a skew type of distribution, notable examples of which are

the response of animals and insects to drugs and hormones. It is clear that the previously reported times of safety at this pressure were dangerously incorrect; in addition, no allowance had been made for individual variation, which is found to be over an enormous range.

Oxygen Tolerance under Water

It has already been emphasized that up to the beginning of these investigations all experiments regarding oxygen tolerance had been carried out by subjects in dry chambers. A series of dives was initiated to discover whether man's tolerance under water was similar to that so far determined in compressed air. The experimental arrangements can be seen in Fig. 3, which is self-explanatory. The respiratory apparatus was a modification of the Davis submarine escape apparatus adapted for four hours' endurance. A light rubberized canvas suit with a soft helmet was worn. The diver was submerged in an open tank and tested for leaks; he then walked to the high-pressure tank and was lowered into the water. The upper hatch was closed and air pressure rapidly applied. The diver was thus exposed to the increased pressure but was under water. On the average, subjects were breathing oxygen, mostly at atmospheric pressure, for ten minutes before arriving at the appropriate experimental depth. Time of compression averaged 90 seconds. The temperature of the water was maintained at 65° F. (18.3° C.). As the depth reading was of the air pressure above the water, the oxygen was breathed at an additional 3 ft. (0.91 m.) of water pressure (see Fig. 3).

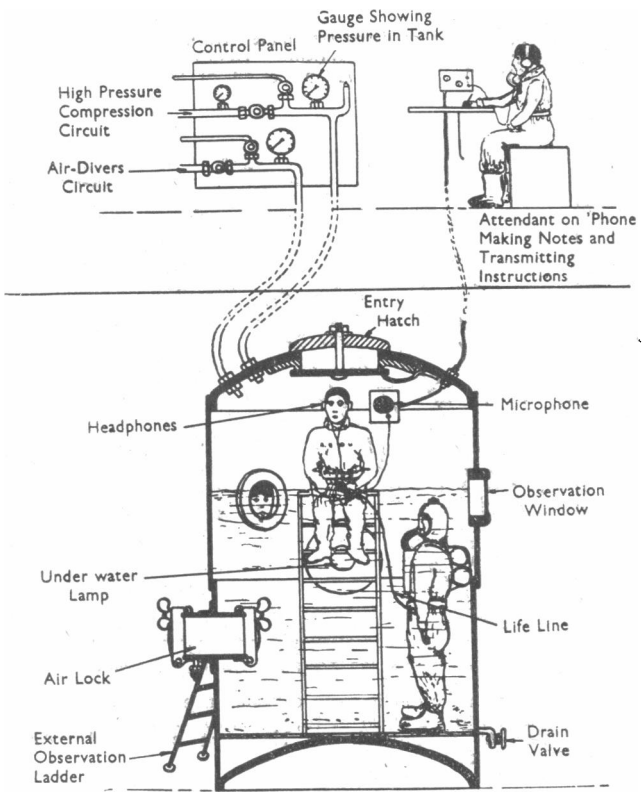

FIG. 3.—Showing wet pressure chamber with diver under water breathing oxygen in self-contained set. Internal and external attendants.

The first series of dives was to 50 ft. (15.2 m.) (2.5 ats. abs.) and the time limit was 30 minutes. One hundred different subjects were employed. If the diver convulsed or had severe symptoms he was hauled out of the water and turned on to air. The mouthpiece acted as an excellent gag during convulsions, and attendants were taught to maintain a good airway. Out of these 100 subjects 26 convulsed, 24 had symptoms, and 50 had no symptoms. Space does not allow details. According to previously accepted figures men were safe breathing oxygen at this depth for at least two hours. The great variability, already demonstrated, makes hard-and-fast rules impossible, but, even allowing for this variation, it was strongly suggested that there was a marked decrease of average tolerance compared with that obtaining in the experiments in compressed air.

A series of dives was therefore carried out to compare the tolerance of subjects in compressed air, and under water, at 60 ft. (18.3 m.) and 90 ft. (27.4 m.) pressure of sea-water. In the first series six subjects were employed. At 60 ft. in the "dry" the subjects tolerated oxygen-breathing for 180, 120, 120, 158½, 101, and 51 minutes, in the first three cases without symptoms. At the same pressure under water the same subjects experienced acute poisoning in 76, 37½, 25, 61, 19, and 12½ minutes respectively. At 90 ft. their performances in the "dry" were 51, 54½, 62, 34½, and 32 minutes, whereas under water they survived only 12, 11, 25½, 18½, and 9½ minutes respectively (one subject indisposed in this series). All these exposures at 90 ft. were terminated by acute symptoms. A larger series of "wet" and "dry" experiments at 90 ft. is shown in Fig. 4. It will be seen from these results that oxygen

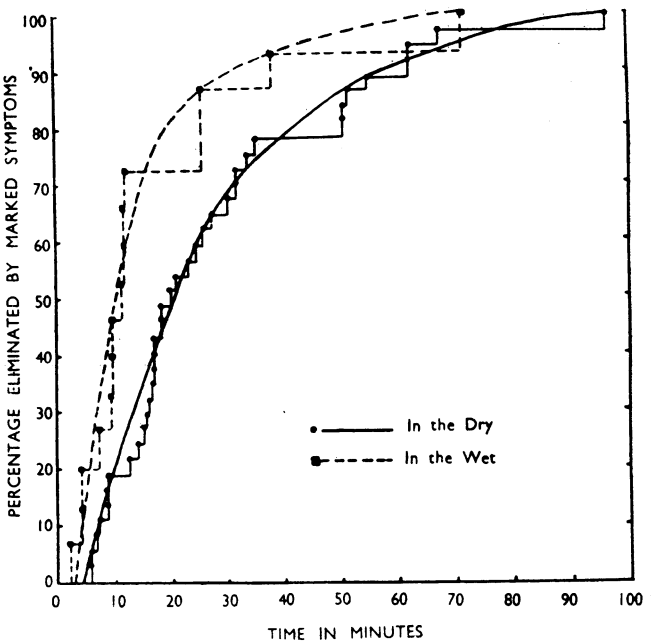

FIG. 4.—Percentage of subjects eliminated by toxic symptoms at 90 ft. (3.73 ats. abs.) breathing oxygen in compressed air and under water (65° F.) in diving-suit. No work performed.

tolerance is greatly decreased when the subject is under water. The enormous importance of this finding need hardly be pointed out. The causes of this impairment remain unknown. There is the added 3 ft. (0.91 m.) of pressure already mentioned, and the diver is breathing pure oxygen in contrast to 95% approximately in the "dry." These two factors are quite inadequate to explain the phenomenon completely. Carbon dioxide accumulation was suspected, as this is known to increase susceptibility to oxygen poisoning in animals (Hill, 1933). Numerous gas analyses negated this possibility. The lack of a rigid helmet, respiratory resistance, the bandaging effect of the suit, the diver's posture, and hydrostatic effects have all been investigated with negative results.

Time–Pressure Relationship for Men Breathing Oxygen Under Water

Next an attempt was made to plot individual curves expressing the relationship of time of survival to pressure. In view of the individual variation it was realized that each diver would have a different curve of tolerance. After a large number of experiments a new factor became increasingly manifest. The tolerance of individual subjects varied from day to day, and it was quite impossible to plot a curve for a single individual. Certain subjects showed this individual variation to a greater degree than others. As with the variation between individuals, no cause for this varying susceptibility to oxygen poisoning could be discovered. In view of these findings, a subject of apparently good resistance was chosen. He dived twice a week over a period of three months to a constant depth of 70 ft. (21.3 m.) in the "wet" (3.12 ats. abs.). He wore the same suit and apparatus on all occasions. All dives were carried out about 11 a.m., after an early and light breakfast. His end-points were usually very definite and his health excellent throughout. The results are given in Table II with end-points and

TABLE II.—*Tolerance of a Single Diver at 70 ft. (21.3 m.) in the Wet over a Period of 90 Days*

Day in Series	Time (mins.)	Symptoms
1	7	Lip-twitching +
7	12½	Nausea +
9	86	Auditory hallucinations, lip-twitching
15	27	Lip-twitching +
17	23	,, +
20	21	,, +
30	28	,, +
34	61	,, +
37	148	Feeling "cross-eyed"; lip-twitching
42	37½	Lip-twitching; coughing
44	96	Lip-twitching; stertorous breathing
48	31½	Lip-twitching +
56	67½	Lip-twitching
70	62½	Lip-twitching; tinnitus; choking sensation; gasping; confusion
72	43	Lip-twitching +
76	41½	Lip-twitching; vertigo; dazzle
78	82	Lip-twitching; dazzle; dyspnoea
80	29½	Lip-twitching; nausea
83	125	Dazzle; amnesia
90	78	Nausea; severe lip-twitching

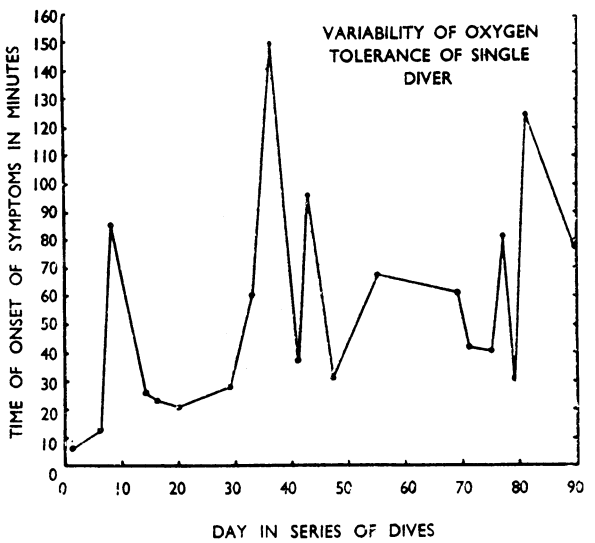

FIG. 5.—Time of exposure causing toxic symptoms in same diver as Table II under sea-water at 70 ft. (65° F.) plotted over a period of 90 days. No work performed.

in Figs. 5 and 6. The curve of distribution obtained was very similar to that showing variation of tolerance in a group. Statistical analysis showed that this subject had a greater variance of toleration than the average. A larger series of experiments confirmed this individual variation. Good examples, in one series, were those divers who survived 100 minutes under water at 50 ft. (15.2 m.). The averages of all their other performances at this depth were 22, 19, and 15 minutes. One subject, who convulsed after 12 minutes at 50 ft., completed 100 minutes at 50 feet

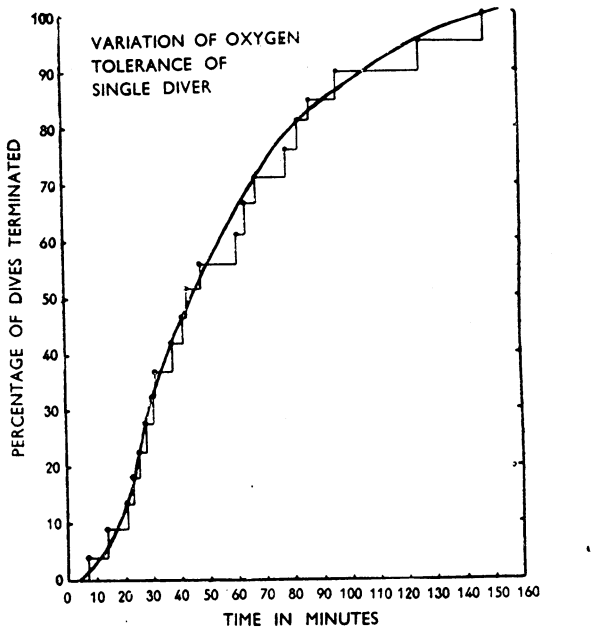

FIG. 6.—Percentage of dives terminated owing to toxic symptoms as a function of duration of exposure. Depth throughout, 70 ft. of sea-water (65° F.). Dives over a period of 90 days. No work performed.

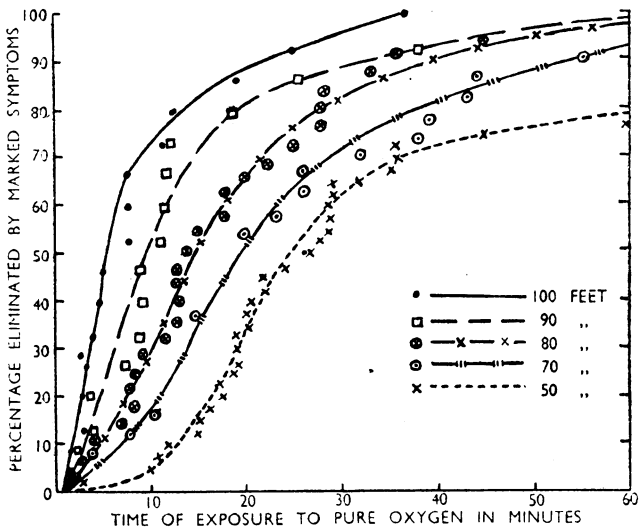

FIG. 7.—Percentage of divers on oxygen, under water, surviving at various times up to 1 hour at 50 ft., 70 ft., 80 ft., 90 ft., and 100 ft. of sea-water, 65° F. throughout. No work performed. Actual end-points plotted.

without symptoms 16 days later. Six days after this he again convulsed at 50 ft. in 32½ minutes. Such findings make it clear that to dive on oxygen to any toxic pressure involves a risk that it is impossible to assess, even if the diver's tolerance has been previously determined.

It now became apparent that the only satisfactory method of assessing oxygen tolerance at various pressures was to employ groups of men for each pressure. Dives were

carried out in the "wet" to a definite end-point by groups of subjects at 50, 60, 70, 80, 90, and 100 ft. in an attempt to obtain a clear overall picture. The results are shown in Fig. 7. The increased toxicity as the depth becomes greater is clearly shown. The highly skew distribution conforms satisfactorily with the Galton-MacAlister law, and it can be demonstrated that all curves in Fig. 7 are the same curve. In other words, the variability of the group is independent of the depth. The coefficient of variation has the huge values of 76–109%, as compared with about 3–4% for such human characters as height, arm length, and alveolar carbon dioxide level. Even more remarkable is the fact that a single diver gave a graph (Fig. 6) of the same type with a coefficient of variation of 67%. This means that a single man may be almost as variable as a group, though this is exceptional. Statistical analysis shows that only 40% of the total variation of oxygen divers is accounted for by day-to-day variation of each individual diver. The other 60% is due to variation between the averages of the different divers.

Maximum Non-toxic Depth under Water at Rest

Next an attempt was made to discover at what pressure, under water, oxygen ceases to cause toxic nervous symptoms that would make free diving dangerous. As work is generally known to impair tolerance the investigation was first carried out without exercise. A large number of dives for a maximum of two hours was performed, and toxic symptoms, and even convulsions, were encountered at 40 ft. (12.2 m.), 35 ft. (10.7 m.), and 30 ft. (9.1 m.). The results may be summarized as follows:

Depth (feet)	No. of Subjects	No. with Symptoms	No. Convulsing
40	29	15	4
35	21	6	1
30	20	3	2
25	28	0	0

It is possible that longer exposures may have caused symptoms at 25 ft. (7.6 m.), but this period is longer than any practical dive on oxygen to this depth. It must be remembered that these divers were exposed to a pressure of oxygen that would occur with a sounding of 32 ft. (9.7 m.). It is a most surprising finding to obtain oxygen convulsions at as low a pressure as 33 ft. (10.1 m.) of sea-water (2 ats. abs.). At such a tension the oxygen dissolved in the blood plasma is inadequate for even basal metabolic requirements, and the haemoglobin is still being actively employed for oxygen transport. Gesell (1923) had suggested that the deactivation of the haemoglobin cycle rendered this substance unavailable for carbon dioxide transport from the tissues and that this caused a severe tissue acidosis. Campbell (1930), by his nitrogen injection technique, had confirmed that there was a remarkable rise of tissue carbon dioxide tension at the usual convulsant levels employed in animal work. However, at the minimal tension causing convulsions in these experiments the carbon dioxide tension was shown by Campbell to be hardly raised. It would appear, therefore, that accumulation of carbon dioxide in the tissues is not the essential cause of oxygen convulsions; and this is in accord with more modern research, which will be discussed later.

Effect of Work on Oxygen Tolerance

It has been generally accepted that work diminishes tolerance to oxygen at increased tensions. However, no reliable experimental data are available. *Il Polombaro* (Italian Ministry of Marine, 1938) gives tables showing a marked effect of work, but these figures appear to be entirely theoretical. A further programme of experimental exposures was therefore carried out in the "wet" with hard work. Controls with the diver resting were also performed. Subjects worked vigorously by lifting a large bag of weights by pulley. Dives were carried out at 50, 40, 35, and 25 ft. These experiments showed conclusively that oxygen tolerance is markedly diminished by work. Figs.

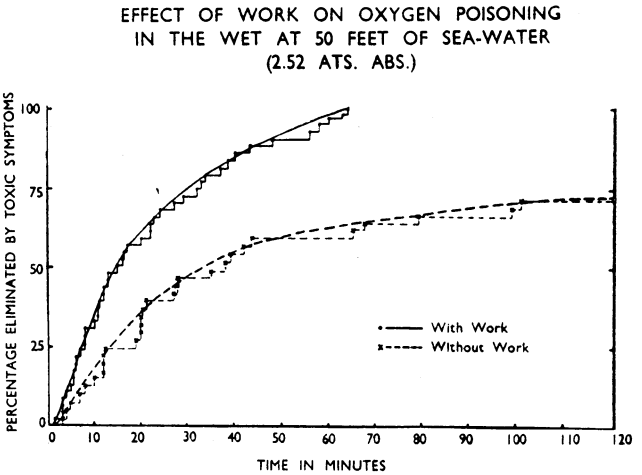

FIG. 8.—Percentage of divers eliminated by toxic symptoms at 50 ft. in the wet (2.52 ats. abs.) during a period of 2 hours, with and without work: 46 divers working, 41 not working. Temperature throughout, 65° F.

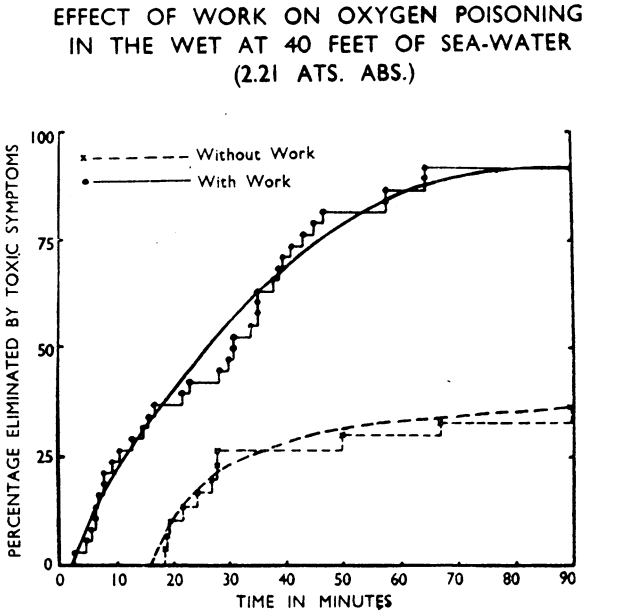

FIG. 9.—Percentage of divers eliminated by toxic symptoms at 40 ft. in the wet (2.21 ats. abs.) during 90 minutes, with and without work: 39 working, 31 not working. Temperature throughout, 65° F.

8 and 9 show the results at 50 ft. and 40 ft. with and without work. Even at 25 ft. toxic symptoms occurred in five out of 18 subjects, though no convulsions were recorded.

The physiological reasons why work reduces oxygen tolerance are not at present definitely known. A further increase of carbon dioxide in the tissues is an obvious possibility, though more reduced haemoglobin is available for carbon dioxide transport. The rise of alveolar carbon dioxide, which is probably very marked when exercising on pure oxygen (to be discussed in later publications), presumably causes cerebral vasodilatation, which may be another adverse factor.

Effect of Temperature on Oxygen Poisoning

Previous work had indicated that the lowering of the environmental temperature increased the oxygen tolerance of small experimental animals (de Almeida, 1934; Campbell, 1937). Three series at 50 ft. were performed, at 87.5° F. (30.8° C.) (steam-heated), at 45° F. (7.2° C.) (ice-cooled), and control exposures at 65° F. (18.3° C.). Divers were allowed to vary their underwear under the suit as the application of this work to operational problems was the first consideration. It is doubted if these exposures could have been tolerated without this variation in clothing. No exercise was carried out. This was advantageous at a higher temperature but disadvantageous to the diver in cold water. The divers complained bitterly of the cold and found the heated dives equally uncomfortable. These experiments showed that oxygen tolerance was equally affected by heat and cold. Although the performances below 30 minutes were only slightly impaired all outstanding performances were eliminated. It is possible that this delayed effect was due to changes in body temperature, as symptoms suggested that this occurred after about 20 minutes.

[*To be concluded, with a bibliography, in next week's issue.*]

THE NICOTINAMIDE SATURATION TEST

BY

P. ELLINGER, Dr.Phil., Dr.Med., F.R.I.C.

AND

S. W. HARDWICK, M.D., M.R.C.P., D.P.M.*

(From the Lister Institute of Preventive Medicine, London, and West Park Hospital, Epsom)

Nicotinamide saturation tests have been carried out by numerous workers (Holt and Najjar, 1943; Ellinger and Coulson, 1944; Ruffin, Cayer, and Perlzweig, 1944; Roberts and Najjar, 1944; Coulson, Ellinger, and Smart, 1945; Ellinger, Benesch, and Hardwick, 1945), based on the daily urinary elimination of nicotinamide methochloride and the response to orally administered nicotinamide. These tests are believed to provide information about the nicotinamide state of the tested person, and, indeed, the findings by Holt and Najjar (1943), Roberts and Najjar (1944), Ellinger, Benesch, and Kay (1945), and Ellinger, Benesch, and Hardwick (1945) show a significantly lower nicotinamide methochloride elimination and response to ingested nicotinamide in pellagrins than in physically fit persons. This is remarkable, since the intake, consumption, and storage of nicotinamide, which determine the nicotinamide state of the body, are probably not the only factors responsible for the extent of the elimination of nicotinamide methochloride. Ellinger and Coulson (1944) mentioned the presence of "methyl-donators" and the efficiency of the methylating mechanism as influencing the extent of nicotinamide methochloride elimination. Malabsorption from the intestines was earlier considered as a possible aetiological factor in pellagra (Ellinger, Hassan, and Taha, 1937), and it was proved to affect the response to ingested nicotinamide in pellagrins but not in healthy persons (Ellinger, Benesch, and Kay, 1945). The recent knowledge of the importance of the intestinal flora for the nicotinamide intake (Ellinger, Coulson, and Benesch, 1944; Ellinger, Benesch, and Kay, 1945; Najjar, Holt, Johns, Medairy, and Fleischmann, 1946), the fact that some intestinal bacteria consume nicotinamide, and the findings by Koser and Baird (1944) that, *in vitro*, some strains of *Pseudomonas* and *Serratia*, and by Benesch (1945) that anaerobes from the intestines, also *in vitro*, destroy nicotinamide, suggest other factors influencing the response to orally administered nicotinamide. It was desirable to study the influence of these various factors on the response to ingested nicotinamide. Unfortunately the number of cases of various liver diseases was so far not large enough for study of the effect of the methylating mechanism, and experiments on rats with induced liver diseases were not yet conclusive (Ellinger, 1946).† But the effect on the response to ingested nicotinamide of the presence of "methyl-donators" and of the route of ingestion could be studied, and this forms the subject of the present communication.

Experimental

Experiment 1.—On 5 healthy persons (2 males, 3 females) and 1 diabetic male, balanced by diet and insulin, of known low methylating capacity (Nos. 1-6). The daily nicotinamide methochloride elimination was measured in 24-hour samples of urine for 3 days without extradietary intake of nicotinamide and, on the 4th day, after the oral ingestion of 100 mg. of nicotinamide at the beginning of the 4th day's urine collection. On the 5th, 6th, and 7th days no urine was collected. On the 7th to 11th days 1 g. of methionine was ingested orally every 12 hours. Urinary nicotinamide methochloride elimination was investigated in 24-hour samples on the 8th to 11th days; no extradietary nicotinamide was administered on the 7th to 9th days, and 100 mg. of nicotinamide was taken by mouth on the 10th day. The experiment was spread over the second half of 1945. All persons continued with their usual work and had their usual food during the experiment.

Experiment 2.—On 5 physically fit inmates of West Park Hospital—1 male and 4 females (Nos. 7-11). The urinary elimination of nicotinamide methochloride was estimated for 14 days—the first 3 days without extradietary administration of nicotinamide, the remaining 11 days after daily ingestion of 100 mg. of nicotinamide at the beginning of the collection period. In addition, 1 g. of methionine was ingested by mouth every 12 hours on the 9th, 10th, and 11th days. The experiment was carried out between March 14 and 31, 1945. All persons in this and the following experiments received the usual hospital diet and were kept in bed or indoors during the experiment.

Experiment 3.—On 8 inmates of West Park Hospital—1 male and 7 females (Nos. 12–19). Four of these were physically fit, one was a physically fit woman who had suffered from pellagra in recent years, and three were pellagrins. The only differences from Experiment 2 were that every second subject was given the daily 100 mg. nicotinamide subcutaneously instead of orally during the whole experiment, while the other half received it by mouth as all subjects in Experiment 2, and the nicotinamide methochloride estimation was continued for one (15th) day after the nicotinamide administration came to an end. The experiment was carried out from April 30 to May 23, 1945.

Experiment 4.—On 5 physically fit and 3 pellagrous female inmates of West Park Hospital (Nos. 20–27). The arrangements in this experiment differ from those of Experiments 2 and 3 in that nicotinamide was administered throughout the experiment to all persons subcutaneously instead of orally, and that 500 mg. (250 mg. twice daily) were given instead of 100 mg. for all 11 days. Urinary nicotinamide methochloride elimination was measured for 15 days, as in Experiment 3. The experiment was carried out between July 10 and 25, 1945.

Experiment 5.—On 9 inmates of West Park Hospital—3 males and 6 females (Nos. 28–36). Six of these were physically fit

* Present address: Medical Superintendent, City of London Mental Hospital, Stone, Nr. Dartford.

† Since this paper was submitted for publication experiments have been carried out showing that experimental liver poisoning in rats causes, after a preliminary rise in nicotinamide methochloride output due to tissue disintegration, a diminished spontaneous nicotinamide methochloride elimination in urine and a diminished response to dosed nicotinamide. Evidence has been obtained also for the elimination of nicotinamide methochloride in the bile and the destruction of the compound by intestinal bacteria *in vitro* (Ellinger, 1947).