own blood. If this is the case, then at present our only hope of preventing such an occurrence lies in active immunization. This should be considered in the light of a possible second wave to the epidemic where the strain of virus may well be enhanced in virulence. As in my cases, the majority of deaths reported in this epidemic occurred in that intermediate group of people between the very young and the very old, and so it would seem desirable that this group should be the first to receive vaccination.

Summary

Three cases of sudden death in young men due to fulminating haemorrhagic influenzal pneumonia are described.

The gross pathological changes present in the lungs of these victims failed to produce correspondingly severe signs and symptoms.

The bacteriological and histological findings suggest that the haemorrhagic pneumonia may have been due primarily to the virus.

ADDENDUM.—Since this paper was written I have seen two further cases of precisely the same nature. The patients were males aged 51 and 24. The latter case is the subject of a medico-legal note on p. 469.

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THE INFLUENZA EPIDEMIC IN ABADAN

BY

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Abadan is a town of about 240,000 people, just under 143,000 of whom are cared for by the medical department of the National Iranian Oil Company. On the whole the climate is hot and dry, the maximum shade temperature varying from 110 to 122° F. (43.3 to 50° C.), and the maximum temperature in the sun rising to 179° F. (81.7° C.) during the period of the influenza epidemic.

All employed persons work in the oil refinery, there being 4,234 classified as "staff" and 26,351 as "labour." The respective figures for "dependants" are 10,351 and 101,716, the vast majority of whom are either wives or children under the age of 20 years. The standard of living of staff is higher than that of labour. Influenza is an unusual disease in Abadan, the great majority of the population at risk never having experienced the condition before.

For the purposes of this paper, the onset of the epidemic is taken as July 14, 1957. There were a few cases during the two weeks prior to that date, but they represent a minute fraction of the total number of persons affected by the illness.

Abadan can be reached by land, sea, and air. It is on the route of several international and national airlines, planes calling on their way to and from Europe, India, and the Far East. Land traffic into Abadan is comparatively small, but a large number of ships, both tankers and merchantmen, arrive from many parts of the world. During the 10 weeks prior to the onset of the epidemic, at least 28 tankers alone arrived in

Abadan from ports further east where there was known to be influenza at the time of their departure. The first of these arrived from Singapore on May 1. It is therefore rather strange that the onset of the epidemic was delayed as long as it was.

The epidemic lasted nine weeks, the total number of cases being 44,921. The weekly figures are shown in

TABLE I.—Weekly Totals

1st week	3,489	4th week	10,210	7th week	387
2nd "	11,302	5th "	4,488	8th "	79
3rd "	12,897	6th "	2,042	9th "	27

Table I. Various measures, such as the closing of indoor cinemas and other gatherings, were taken, but no vaccine was used.

On the first day of the epidemic a large proportion of the patients were admitted to hospital, but thereafter only those whose condition was poor or who were suffering from complications were admitted, the remainder being treated as out-patients. Altogether 467 were admitted—412 with influenza and 55 with a complication.

When the patients were first seen the diagnosis was made on the presence of fever with one or more of the common symptoms. Details of the large number of patients treated in their own homes is not exact, and in many instances the total duration of the illness is not known. Treatment with aspirin, codeine, and cough mixtures was given to out-patients and in-patients suffering from uncomplicated influenza. Of the 44,483 whose initial illness was not treated in hospital, 55 were subsequently admitted suffering from a complication. Table II shows the number affected and the percentage

TABLE II

		0-19 Years	20-60 Years	Total
Staff	No. affected ..	1,093	1,780	2,873
	Total population ..	6,441	8,468	14,909
	Percentage affected ..	17.0	21.0	19.3
Labour	No. affected ..	25,502	16,546	42,048
	Total population ..	75,365	52,702	128,067
	Percentage affected ..	33.7	31.4	32.8
Total	No. affected ..	26,595	18,326	44,921
	Total population ..	81,806	61,170	142,976
	Percentage affected ..	32.5	29.9	31.4

incidence of the disease in children and adults in the staff and labour groups, from which it can be seen that labour was affected to a much greater degree than staff but that age made little difference.

Patients Admitted Suffering from Uncomplicated Influenza

The 412 patients in this group were selected for admission because of the severity of the attack or for convenience in the case of nursing staff. There were 60 staff employed (29 males and 31 females), 127 labour employed (125 males and 2 females), 59 staff dependants (33 males and 26 females), and 166 labour dependants (69 males and 97 females). Twenty-seven patients subsequently developed a complication, all but one while in hospital. The latter patient was discharged, but a day or two later he was re-admitted suffering from pneumonia. Table III shows the percentages of patients—children and adults, staff and

TABLE III.—Percentage of Patients with Uncomplicated Influenza Admitted to Hospital

	0-19 Years	20-60 Years
Staff and dependants	5.76	3.15
Labour	0.47	0.86

TABLE IV.—*Patients Admitted with Uncomplicated Influenza*

	Duration of Fever Before Admission (Days)											
	1	2	3	4	5	6	7	8	9	10	11	12
Total duration of fever (days) { Max.	9	9	12	8	9	13	10	13	—	12	—	14
Min.	2	3	4	5	6	7	8	9	—	11	—	14
Average total duration of fever (days) ..	3.95	4.59	5.45	5.78	7.23	8.33	8.57	11.0	—	11.67	—	14
duration of fever after admission (days) ..	2.95	2.59	2.45	1.78	2.23	2.33	1.57	3.0	—	1.67	—	2.0
No. of patients ..	85	102	60	27	13	15	7	2	—	3	—	1
Total duration of illness (days) { Max.	17	17	21	14	16	24	15	20	—	30	—	29
Min.	3	4	4	6	8	9	9	16	—	13	—	14
Average total duration of illness (days) ..	7.02	7.64	8.75	9.07	9.0	13.0	12.0	18.0	—	18.8	—	19.25
No. of patients ..	86	102	60	28	15	17	7	2	—	5	—	4
Stay in hospital after fever sub-	12	13	14	10	8	10	8	11	—	18	—	3
sided (days) { Max.	0	0	0	1	1	0	0	3	—	6	—	3
Min.	0	0	0	1	1	0	0	3	—	6	—	3
Average stay after fever subsided (days) ..	2.93	3.19	3.18	3.44	3.33	3.75	3.43	7.0	—	11.0	—	3
No. of patients ..	84	101	60	27	13	16	7	2	—	3	—	1

labour—who were suffering from an attack of uncomplicated influenza severe enough to warrant admission to hospital.

In the second to fifth weeks inclusive, during which time 85% of the total cases occurred, the percentage of patients suffering from uncomplicated influenza who were admitted varied between 0.37 and 0.72, suggesting that the severity of the attacks did not vary greatly as the epidemic progressed.

On admission patients gave a history of fever and other symptoms, the duration of which varied. Fever was complained of in 100%, headache in 74%, cough in 69%, generalized aching in 61%, sore throat in 35%, and vomiting in 13%. Haemoptysis was not a common occurrence during the acute attack, but was often seen during the two or three days after the fever had subsided, the blood being dark red or black.

The period of fever before admission varied from 1 to 12 days, and after admission from 1 to 9 days, while the overall duration of fever varied between 2 and 14 days. Table IV shows the relationship between the period of fever before admission, the average total duration of fever, and the average period of fever after admission to hospital. From this it can be seen that, while the total duration of fever increased with the period of fever prior to admission, the duration of fever after admission remained remarkably constant.

After the fever subsided the patients remained in hospital for a varying period of time. The middle part of Table IV relates the average stay in hospital after cessation of fever to the duration of fever before admission, and it can be seen that the latter had no effect on the duration of debility following the fall in temperature. From the lower part of Table IV it can be seen that the total duration of the illness increased steadily with the period of fever before admission.

Complications

Altogether 82 patients (50 males, 32 females) suffering from influenza developed a complication. In 27 instances this developed in patients already admitted for the primary illness, the remaining 55 being admitted suffering from the complication, but giving a history of influenza immediately before its onset. The incidence of complications in the epidemic as a whole was 0.18%. Twelve patients were staff and 70 were labour. In the different groups the rates were: (a) staff 0–19 years, 0.92%; 20–60 years, 0.11%; (b) labour 0–19 years, 0.12%; 20–60 years, 0.24%.

Of the 412 patients admitted for severe influenza, 27 developed a complication, an incidence of 6.6%, whereas of the 44,509 who were not considered to be ill enough to warrant admission and who were treated as out-patients 55 were later admitted—an incidence of 0.12%.

The symptoms of the primary illness were similar to those in uncomplicated cases—namely, fever in 100%, cough in 78%, headache in 55%, generalized aching in 45%,

sore throat in 16%, and vomiting in 16%. The incidence of complications varied from 0.1 to 0.34% over the first six weeks of the epidemic but in no definite manner.

Of the 82 patients, 35 developed bronchitis, 44 pneumonia, one jaundice, one otitis media, and one cerebral sinus thrombosis. The last-named patient and four suffering from pneumonia died in hospital, four of them having the complication on admission.

Admitted with Uncomplicated Influenza.—In six instances there was an afebrile period of one day before the onset of the complication, in a further six the temperature was normal for two days, and in one for three days. Six patients had been admitted on the first day of the primary illness, 11 on the second, four on the third, and four on the fourth to eighth days, while in two instances the day of onset was not known. Of these 27 patients, 15 developed bronchitis, 11 pneumonia, and one otitis media.

Admitted Suffering from a Complication.—In the majority of the 55 patients in this group it was not possible to discover whether there had been an afebrile period in the illness or the exact day on which the complication had started. The day of onset of the primary illness, however, was usually known.

TABLE V.—*Complications: Age and Sex Distribution*

	0–19 Years		20–60 Years		Total
	M	F	M	F	
Bronchitis ..	8	10	17	—	35
Pneumonia ..	8	11	17	8	44
Jaundice ..	—	1	—	—	1
Otitis media ..	—	1	—	—	1
Cerebral sinus thrombosis ..	—	1	—	—	1
Total ..	16	24	34	8	82
Staff total ..	4	6	2	0	12
Labour total ..	12	18	32	8	70

Table V shows the age and sex distribution of the complications. The patient who developed jaundice was a girl aged 7 years who was admitted to hospital on the seventh day of her illness, which had started with fever, headache, and generalized aching. This lasted for three days. She was then afebrile for two days, after which she again developed fever, headache, abdominal pain, and vomiting. On admission she looked ill, temperature 104° F. (40° C.), pulse 140, tongue coated, throat inflamed, spleen palpable, very obvious icterus of the skin and conjunctivae, and leucocytes 9,000/c.mm. The duration of the second period of fever was six days, during which time the jaundice gradually faded. She was discharged after 12 days in hospital.

Treatment of Complications

Treatment for complications was started either on admission or when diagnosed in hospital. Except in some of the patients suffering from bronchitis and the patient with jaundice, this consisted of an antibiotic. Table VI records

TABLE VI.—*Drugs Used in Treatment*

	Penicillin	Chloramphenicol	Chlorotetracycline	Nil	Total Cases
Bronchitis ..	7	19	—	9	35
Pneumonia ..	2	36	2	—	40
Otitis media ..	—	1	—	—	1
Jaundice ..	—	—	—	1	1
Total ..	9	56	2	10	77

the number of patients treated with the different drugs, the five patients who died being excluded. Penicillin dosage varied from 3 million units in six days to 13 million units in 16 days, and that of chloramphenicol from 3 g. in three days to 24 g. in eight days. In 69 of the patients suffering from bronchitis or pneumonia, the exact duration of the fever following onset of treatment was known, and the number of patients in the different groups is shown in Table VII. The total duration of the illness from onset

TABLE VII.—*Persistence of Fever*

	Treatment	Duration of Fever After Start of Treatment (Days)								Total Cases
		1	2	3	4	5	6	7	8	
Bronchitis {	No antibiotic ..	—	1	3	1	2	—	1	—	8
	Penicillin ..	2	2	—	1	1	—	—	—	6
	Chloramphenicol ..	3	6	—	2	2	—	—	—	19
Pneumonia {	Penicillin ..	1	—	—	—	1	—	—	—	2
	Chloramphenicol ..	7	11	6	5	3	1	—	1	34
Total ..		13	20	15	9	9	1	1	1	69

TABLE VIII.—*Duration of Illness*

Complication	Admitted as:	Total Duration of Illness (Days)								Total Cases
		0-5	6-10	11-15	16-20	21-25	26-30	30+	Unknown	
Bronchitis {	Influenza ..	—	6	8	—	—	—	—	1	15
	Complication ..	—	8	4	3	2	—	—	2	20
Pneumonia {	Influenza ..	1	4	3	3	1	—	—	—	11
	Complication ..	—	11	9	2	3	1	1	—	29
Jaundice	Complication ..	—	—	—	1	—	—	—	—	1
Otitis media	Influenza ..	—	—	1	—	—	—	—	—	1
Totals {	Influenza ..	1	10	12	3	1	—	—	1	27
	Complication ..	—	19	13	6	5	—	2	3	50
	Both together	1	29	25	9	6	1	2	4	77

of influenza to discharge from hospital after treatment of the complication varied greatly in different patients, and the numbers in the various groups are recorded in Table VIII.

Deaths

Patient 1.—A girl aged 2½ years was admitted with a history of fever, non-productive cough, and abdominal pain for the previous seven days. The general condition was found to be very poor; temperature 104.2° F. (40.1° C.), pulse 120 and very weak; dyspnoeic, cyanosed, and with widespread bilateral crepitation in the lungs. Chloramphenicol was given intramuscularly, but the child died six hours after admission.

Patient 2.—A woman aged 45 was admitted with a history of fever, non-productive cough, abdominal pain, vomiting, and severe headache for the previous two weeks. Her general condition was poor; temperature 101° F. (38.3° C.), pulse 120, and evidence of bronchopneumonia. She was treated with chloramphenicol by mouth and later intramuscularly. Her condition remained about the same for the next five days, and she died six days after admission.

Patient 3.—A girl aged 2 years was admitted with a history of headache and fever for the previous seven days. Despite treatment with chloramphenicol, given because *H. influenzae* predominated on culture of the throat swab, her general condition deteriorated and she died of bronchopneumonia three days after admission. She was a staff dependant.

Patient 4.—A man aged 55 had influenza, from which he recovered. Four days later he again became ill, with headache, cough, fever, and abdominal pain. On examination he was dehydrated, fibrillating, and with widespread bilateral crepitations in the lungs. He was given chloramphenicol, 2 g. initially, followed by 1 g. intramuscularly six-hourly, but he gradually deteriorated, became cyanosed and severely dyspnoeic, and died seven days after admission.

Patient 5.—A girl aged 10 gave a history of fever, headache, cough, little sputum, and vomiting for an unknown period of time. On admission, treatment with chloramphenicol, 500 mg. six-hourly, was started, but two days later she became comatose and was found to have some neck stiffness, pin-point pupils, variable strabismus, and flaccid limbs; all reflexes were absent. The left plantar response was extensor, the right not elicited. There was marked bilateral papilloedema but no evidence of sepsis of the face, ears, or scalp. Lumbar puncture yielded a normal fluid under very high pressure, and a diagnosis of cerebral sinus thrombosis was made. Streptomycin was added to the chloramphenicol, now given intramuscularly, and the next day she was more alert and reacted quickly to painful stimuli, moving all four limbs, but the papilloedema was unaltered. 15 ml. of C.S.F. was removed, and the next day the temperature had fallen to 100° F. (37.8° C.) and she was able to obey simple commands. 10 ml. of C.S.F. was removed. All specimens of C.S.F. showed no abnormality other than raised pressure. On the following day she again became comatose, the temperature rose to 105° F. (40.6° C.), spasticity developed in all four limbs, and she died within a few hours. Post-mortem examination was refused by the parents.

Discussion

Following a period of two weeks, during which time there were sporadic cases only, the epidemic was an explosive one, there being nearly 3,500 people affected during the first week and the figure rising to almost 13,000 during the third week. It is not possible to be certain of the source of infection, but it is most likely that it was ships arriving from ports where influenza was present. It is surprising that the epidemic did not start in Abadan much earlier, as at least 28 ships arrived from already infected ports during the previous 10 weeks.

Of the 143,000 people under consideration, 31.4% developed influenza. Labour was much more affected than staff in the ratio of 32.8 to 19.3. Staff children were a little less affected than staff adults, and labour children a little more than labour adults, but the differences were not very marked. It is possible that more crowded living conditions caused the higher incidence amongst labour.

Table III indicates that the percentage of patients admitted was much greater among staff than among labour. This difference cannot be explained on the availability of beds, because at no time during the epidemic were all beds filled. Male labourers may have tended to stay at work for financial reasons. Labour patients were admitted to the Isolation Hospital, whereas staff were admitted to the General Hospital. The Isolation Hospital is feared by the population in general—a fear dating from the days when smallpox and typhus were more prevalent, and perhaps from the fact that tuberculosis is treated there to-day. Nursing staff were treated in hospital rather than in the Nurses' Home. These considerations tend to reduce the apparent discrepancy in the severity of the attack in staff and labour, the impression being that little difference existed at all.

The patients who were admitted were obviously ill. The temperature was usually 103–104° F. (39.4–40° C.) and up to 106° F. (41.1° C.), especially in small children. It is not thought that heat disorder played a part, because, although it was a hot summer, the incidence of heat hyperpyrexia was lower than in previous years, both in the local population and in the ships' crews. Sore throat was present in 35% of patients. This was also found to be common in Singapore, though in Kuwait (McCreadie, 1957) it was unusual.

Table IV shows that the total duration of fever and of the illness as a whole increased with the period of fever before admission but that the period of fever after admission and the subsequent period of debility remained fairly constant at about two to three and three to four days respectively. The total duration of the illness was seven to nine days in the majority of patients admitted. Exact figures are not available for the large number of patients treated as out-patients, but the impression is that the duration was less than in those admitted to hospital.

Complications, mainly bronchitis and pneumonia, occurred in 0.18% of all patients, but were much more common in those who had been admitted because of a severe attack of influenza (6.6%) than in those whose primary illness did not warrant admission (0.12%). Those who developed the complication in hospital had not been ill for a longer than average period before admission, so that it would appear that it was the severity of the primary illness rather than its duration that was important. It might have been expected that labour, with a lower standard of living, would have been more prone to complications, but this was not the case. Staff as a whole had a complication rate of 0.42% and labour of 0.17%, the discrepancy being due to the high rate of 0.92% in staff under the age of 20. Males developed complications more often than females, the ratio being 50:32, and younger children more often than older children.

Because of the predominance of *H. influenzae* in sputum cultures, chloramphenicol was the antibiotic most used in the treatment of respiratory complications. The response to treatment was moderately good, the temperature reaching normal within five days in the vast majority. In the case of bronchitis this was so, whether an antibiotic was used or not. The total duration of the illness varied from one to three weeks with a few exceptions, and this was only slightly longer in those admitted suffering from the complication than in those in whom it developed in hospital.

The five patients who died were all in poor condition on admission. With the exception of the child who developed cerebral sinus thrombosis, all were admitted suffering from the complication and had been ill for one to two weeks before admission. The death rate in the epidemic was therefore about 1 in 9,000. Reports from other parts of the world have shown that the case fatality has varied greatly from place to place. In Malaya it was reported at about 1 in 40,000, and in West Pakistan at 1 in 46,000, whereas in the Philippines it was as high as 1 in 220. In Aden (Fawdry, 1957), the deaths attributable directly or indirectly to the influenza epidemic were estimated at about 200, a case fatality rate of 1 in 350. There seems to be no very good reason for the great difference in the mortality in Aden and Abadan, which have similar climates and similar standards of living.

Up to the time of writing, the diagnosis of pulmonary tuberculosis has been made for the first time in 14 patients who had recently suffered from influenza. The history was the same in them all—the cough did not clear up after the temperature had subsided. So far, a relapse of pulmonary tuberculosis in a person recently affected by influenza has not been encountered. It is interesting that the daily out-patient attendance for all conditions is higher now after the influenza epidemic than at the same time in previous years. This is partly due to the malaria epidemic in progress at present, but, even allowing for this, the attendances are greater than usual.

Conclusions

The influenza epidemic in Abadan started suddenly on July 14, 1957, and involved 31.4% of the 143,000 persons associated with the National Iranian Oil Company. The lower-income groups were more affected than the higher, but there was little difference in the incidence or severity of the attack in the two sexes or at different ages.

The attack consisted of an acute febrile illness with marked constitutional upset, cough, and, quite fre-

quently, a sore throat. Going to bed early in the illness shortened its duration but had little effect on the period of fever after hospitalization or on the subsequent period of debility. The attack was not as short as has been suggested from other reports, the average duration of the uncomplicated illness being seven to nine days in those whose condition warranted admission to hospital.

Complications were mainly bronchitis and pneumonia, the incidence being very much greater in those patients who had a severe attack of influenza. The overall incidence was 0.18%. The response to treatment was fairly prompt. The case fatality of the epidemic was 1 in 9,000, four of the five deaths occurring in patients admitted for the complication. All five were in poor condition or had been ill for one or two weeks before admission.

The epidemic has resulted in an increase in the general ill-health of the community, and several patients have subsequently been found to be suffering from pulmonary tuberculosis.

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ROLE OF INSULIN IN ACUTE HYPOLYCAEMIC ACTION OF TOLBUTAMIDE

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The mode of action of the sulphonylureas* as hypoglycaemic agents is unknown. They are believed by some to act by increasing the amount or the effectiveness of insulin. Others believe that their effect is unlike and independent of insulin. Since much of the experimental work is contradictory, some of the experiments which clearly differentiate these opposing views need re-evaluation.

There is evidence, widely accepted, that insulin increases the uptake of glucose by tissues. This effect of insulin can be demonstrated *in vivo* by an increase in the difference between the arterial and venous glucose concentrations (A.-V. difference) in extremities, provided there is no change in peripheral blood flow, and *in vitro* by an increase in the glucose uptake of the isolated rat diaphragm. In studies of the effect of the sulphonylureas on arterial-venous blood-sugar differences an increase has been demonstrated by Goetz *et al.* (1956) but not by Purnell *et al.* (1956). Incubation of the rat dia-

*In this paper the term "sulphonylurea" refers to either 1-butyl-3-*p*-tolylsulphonylurea (tolbutamide) or 1-butyl-3-sulphanilylurea (carbutamide), since these drugs are generally held to have similar metabolic effects.